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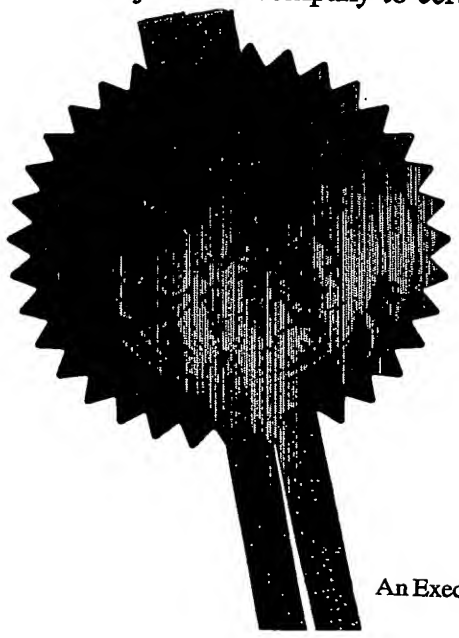

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Dated 10 February 2003

Patents Form 1/77

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
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Gwent NP9 1RH

1. Your Reference — **AP/PI4557**

2. Patent application number *(The Patent office will fill in this part)* — **08 FEB 2002** **0203021.1**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

GLAXO GROUP LIMITED
GLAXO WELLCOME HOUSE
BERKELEY AVENUE
GREENFORD
MIDDLESEX
UB6 ONN
GB

00473587003
Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its corporation — **GB**

4 Title of the invention — **CHEMICAL COMPOUNDS**

5 Name of your agent *(if you know one)* — **PETER I DOLTON**

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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Patents ADP number *(if you know it)*

08321846001

6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

YES

See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	-
Description	37
Claim(s)	3
Abstract	1
Drawing(s)	-

10. If you are also filing any of the following, state how many against each item

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. **I/We request the grant of a patent on the basis of this application**

P. I. Dolton

Signature PETER I DOLTON. 8 February 2002
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

JEAN HARNEY
020 8047 4420

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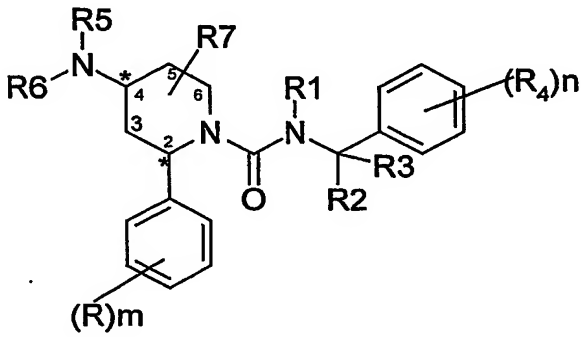
Chemical Compounds

The present invention relates to amine derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use.

In particular the invention relates to novel compounds, which are potent and specific antagonists of tachykinins, including substance P and other neurokinins.

Thus the present invention provides compounds of formula (I)



(I)

wherein

R represents halogen or C_{1-4} alkyl ;

R_1 represents hydrogen or C_{1-4} alkyl;

R_2 represents hydrogen, C_{1-4} alkyl or R2 together with R_3 represents a C_{3-7} cycloalkyl;

R_3 represents hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl or C_{3-6} alkenyl ; or R_1 and R_3 together with nitrogen and carbon atom to which they are attached respectively represent a 5 to 6 membered heterocyclic group;

R_4 represents trifluoromethyl, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethoxy or halogen;

R_5 represents hydrogen, phenyl, C_{3-7} cycloalkyl, $CONR_8R_9$, a saturated 5 to 7 membered heterocyclic group, a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or R_5 represents a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms, or R_5 is C_{1-6} alkyl optionally substituted by one or two groups selected from fluorine, phenyl hydroxy, amino, dimethylamino, aminocarbonyl, C_{1-4} alkoxy or trifluoromethyl;

R_6 represents hydrogen or C_{1-4} alkyl;

R_7 represents hydrogen, a halogen, a C_{1-4} alkyl or COR_{10};

R_8 and R_9 are independently hydrogen or C_{1-4} alkyl;

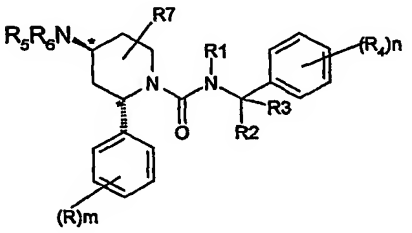
R_{10} represents hydrogen, hydroxy, amino, methylamino, dimethylamino a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms; m or n are independently zero or an integer from 1 to 3; and pharmaceutically acceptable salts and solvates thereof.

Suitable pharmaceutically acceptable salts of the compounds of general formula (I) include acid addition salts formed with pharmaceutically acceptable organic or inorganic acids, for example hydrochlorides, hydrobromides, sulphates, alkyl- or arylsulphonates (e.g. methanesulphonates or p-toluenesulphonates), phosphates, acetates, citrates, succinates, tartrates, fumarates and maleates.

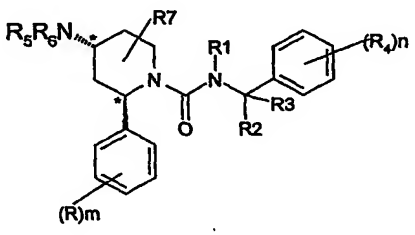
The solvates may, for example, be hydrates.

References hereinafter to a compound according to the invention include both compounds of formula (I) and their pharmaceutically acceptable acid addition salts together with pharmaceutically acceptable solvates.

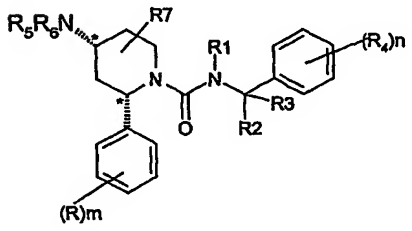
It will be appreciated by those skilled in the art that the compounds of formula (I) contain at least two chiral centres (namely the carbon atoms shown as * in formula (I)) and these may be represented by the formulae (1a, 1b, 1c and 1d)



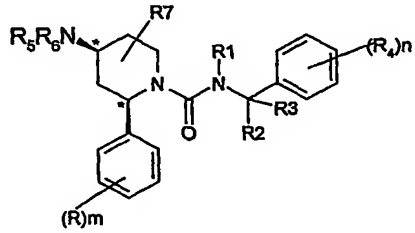
1a



1b



1c



1d

The wedge shaped bond indicates that the bond is above the plane of the paper. The broken bond indicates that the bond is below the plane of the paper.

The configuration of the two chiral carbon atoms of the piperidine ring shown in formulae 1a and 1b is hereinafter referred to as anti-configuration and in formulae 1c and 1d as the syn configuration.

Further asymmetric carbon atoms are possible in the compound of formula (I).

Thus, when R_2 is C_{1-4} alkyl, a C_{3-7} cycloalkyl or a C_{3-6} alkenyl group and R_3 is hydrogen, or when R_2 is hydrogen and R_3 is C_{1-4} alkyl, C_{3-7} cycloalkyl or a C_{3-6} alkenyl group the compounds of formula (I) possess at least three asymmetric carbon atoms.

Furthermore , when R_7 is a halogen atom , a C_{1-4} alkyl or a COR_{10} group,

and when R_2 is C_{1-4} alkyl, a C_{3-7} cycloalkyl or a C_{3-6} alkenyl group and R_3 is hydrogen, or when R_7 is a halogen atom , a C_{1-4} alkyl or a COR_{10} group and when R_2 is hydrogen and

R_3 is C_{1-4} alkyl, C_{3-7} cycloalkyl or a C_{3-6} alkenyl group the compounds of formula (I) possess four asymmetric carbon atoms.

It is to be understood that all enantiomers and diastereoisomers and mixtures thereof are encompassed within the scope of the present invention.

The term C_{1-4} alkyl as used herein as a group or a part of the group refers to a straight or branched alkyl group containing from 1 to 4 carbon atoms; examples of such groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, 1 methylethyl or 2-methyl propyl.
The term C_{1-6} alkyl is meant to include C_{1-4} alkyl and the higher homologues thereof having 5 or 6 carbon atoms such as for example pentyl, 2-methylbutyl, hexyl, 2-methylpentyl or dimethylpropyl.

The term C_{3-6} alkenyl group refers to a straight or branched alkenyl group containing from 3 to 6 carbon atoms; examples of such groups include 2-propenyl, 1 propenyl, isopropenyl, 2-butenyl, 2-pentenyl, 2-hexenyl and the like.

When R_1 and R_3 together with nitrogen and carbon atom to which they are attached respectively represent a 5 to 6 membered heterocyclic group this group is saturated or contains a single double bond. This may be a 3,6-dihydro-2H-pyridin-1yl, a piperidin-1-yl or a pyrrolidin 1-yl group.

When R_5 is a 5 or 6 membered heteroaryl group according to the invention they include furanyl, thiophenyl, imidazolyl, thiazolyl, oxazolyl, pyridyl or pyrimidinyl.

When R_5 is saturated 5 to 7 membered heterocyclic group examples of this group include pirrolidinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl, 1.3 dioxolan-yl or morpholin-yl.

The term C_{3-7} cycloalkyl group means a non aromatic monocyclic hydrocarbon ring of 3 to 7 carbon atom such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The term halogen refers to a fluorine, chlorine, bromine or iodine atom.

The term C_{1-4} alkoxy group may be a straight chain or a branched chain alkoxy group, for example methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy or methylprop-2-oxy.

When R represents halogen this is suitably chlorine or more preferably fluorine or when R is C_{1-4} alkyl this is suitably methyl or ethyl wherein m is 0 or an integer from 1 to 2.

Suitable values for R_1 or R_2 include hydrogen, a methyl, an ethyl or a propyl group.

Suitable values for R_3 include hydrogen, a methyl, an ethyl, 2-propenyl or cyclopropyl.

R_1, R_2 and R_3 are all suitably hydrogen or all suitably are methyl group or suitably one of the R_1 or R_2 is a methyl group and the other is hydrogen and R_3 is methyl or hydrogen.

Suitable values for R_4 include a methyl, an ethyl, a trifluoromethyl or a halogen (i.e. chlorine, fluorine) group.

When R_5 is C_{1-6} alkyl optionally substituted this is suitably adimethylpropyl group a methyl optionally substituted by a phenyl or an amino carbonyl group, an ethyl group optionally substituted by one or two a phenyl, a fluorine, a hydroxy, an amino, a methoxy or a trifluoromethyl group.

R is preferably a halogen (e.g. fluorine) and /or C_{1-4} alkyl (e.g. methyl) and m is preferably zero or an integer from 1 to 2.

R_1 is preferably a hydrogen or methyl.

R_2 is preferably hydrogen or methyl.

R_3 is preferably hydrogen , methyl or cyclopropyl.

R_4 is preferably trifluoromethyl, methyl or chlorine.

R_5 is preferably hydrogen , cyclopropyl, cyclobutyl, piperidyl, 1.3 dioxolanyl, dimethylpropyl , methyl (optionally substituted by a phenyl or an amino carbonyl group), ethyl (optionally substituted by a phenyl, a fluorine, a hydroxy, an amino, a methoxy or a trifluoromethyl group).

R_6 is preferably hydrogen or methyl.

R_7 is preferably hydrogen, fluorine or methyl.

A preferred class of compounds of formula (I) are those wherein R is a halogen (e.g. fluorine) and /or a C_{1-4} alkyl (e.g. methyl) group, wherein m is 0, 1 or 2. More preferably m is 2. Within this class those wherein R is at the 2 and 4 position are particularly preferred.

Compounds of formula (I) wherein R_4 is a trifluoromethyl group and n is 2 represent a preferred class of compounds and within this class R_4 is preferably at the 3 and 5 position.

Also a preferred class of compounds of formula (I) are those wherein R_1, R_2 or R_3 represent independently hydrogen or a methyl group.

A further preferred class of compounds of formula (I) are those wherein R_1 or R_2 represent independently hydrogen or a methyl group and R_3 is hydrogen.

A particularly preferred group of compounds of formula (I) is that R is halogen and/or methyl, R_4 is trifluoromethyl at the 3 and 5 position, R_1, R_2 R_6 or R_3 are independently hydrogen or methyl, R_5 is a hydrogen atom, a cyclopropyl, a cyclobutyl, a piperid-4-yl, a 1,3-dioxolan-2-yl, a dimethylpropyl, a methyl optionally substituted by a phenyl or an amino carbonyl group, an ethyl group optionally substituted by a trifluoromethyl, fluorine or a methoxy group.

Suitable compounds according to the invention are:
4-(R,S)-2,2,2-Trifluoroethyl)-amino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;
4-(S)-(2,2-Dimethyl-propylamino)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;
4-(S)-Ethylamino-2-(R)-4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;
4-(S)-Dimethylamino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide ;
4-(S)-Dimethylamino-2-(R)-4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide;
4-(S)-(2-Fluoroethyl)-amino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis)-trifluoromethyl-phenyl)-ethyl]-methylamide ;
4-(S)-(N-2-Fluoroethyl-N-methylamino)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide;
4-(S)-(2-Fluoro-ethylamino)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide;
2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-(2-methoxyethylamino)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;
2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-methylamino-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;
2-(4-Fluoro-2-methyl-phenyl)-4-methylamino-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide;
4-(S)-Cyclobutylamino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis)-trifluoromethyl-phenyl)-ethyl]-methylamide;
4-(S)-Cyclopropylamino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;
2-(R)-(4-Fluoro-2-methyl-phenyl)-4-[methyl-(1-methyl-piperidin-4-yl)-amino]-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;

4--Benzylamino-2-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide;
4-[(1,3-Dioxolan-2-yl)-methyl]-amino-2-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide;
4-(S)-(Carbamoylmethyl-amino)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide;
and enantiomers, pharmaceutically acceptable salts and solvates thereof.

Particularly preferred compounds according to the invention are:
4-(S)-Dimethylamino-2-(R)-4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride;
4-(S)-Dimethylamino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide hydrochloride;
4-(S)-(2-Fluoroethylamino)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide hydrochloride
4-(S)-(N-2-Fluoroethyl-N-methylamino)-2-(R)-4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide hydrochloride

The compounds of the invention are antagonists of tachykinins, including substance P and other neurokinins, both in vitro and in vivo and are thus of use in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins.

The compounds of the present invention have also activity as serotonin reuptake inhibitors.

NK_1-receptor binding affinity has been determined in vitro by the compounds' ability to displace [3H] - substance P (SP) from recombinant human NK_1 receptors expressed in Chinese Hamster Ovary (CHO) cell membranes.
CHO cell membranes were prepared by using a modification of the method described by Dam T and Quirion R (Peptides, 7:855-864, 1986). Thus ligand binding was performed in 0.4 ml of 50 mM HEPES, pH 7.4, containing 3 mM $MnCl_2$, 0.02% BSA, 0.5 nM [^{3}H]Substance P (30÷56 Ci/mmol, Amersham), a final membrane concentration of 25 µg of protein/ml, and the test compounds. The incubation proceeded at room temperature for 40 min. Non-specific binding was determined using excess of Substance P (1 µM) and represents about 6% of the total binding.
Compounds of the invention were further characterised in a functional assay for the determination of their inhibitory effect. Human-NK_1-CHO cells were stimulated with Substance P and the receptor activation was evaluated by measuring the accumulation of cytidinediphosphodiacylglycerol (CDP-DAG), which is the liponucleotide precursor of phosphatidylinositol diphosphate. CDP-DAG accumulates in the presence of Li^+ as a consequence of the receptor mediated activation of phospholipase C (PLC) (Godfrey, Biochem. J., 258:621-624, 1989). The method is described in detail by Ferraguti et al. (Mol. Cell. Neurosci., 5:269-276, 1994).

The action of the compounds of the invention at the NK_1 receptor may be determined by using conventional tests. Thus the ability to bind at the NK_1 receptor was determined using the gerbil foot tapping model as described by Rupniak & Williams, Eur. J. of Pharmacol., 1994.

Compounds of the invention have also been found to exhibit anxiolytic activity in conventional tests. For example in marmoset human threat test (Costall et al., 1988).

Compounds of the invention may be useful in the treatment of CNS disorders in particular in the treatment or prevention of major depressive disorders including bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, the treatment of anxiety and the treatment of panic disorders. Other mood disorders encompassed within the term major depressive disorders include dysthymic disorder with early or late onset and with or without atypical features, neurotic depression, post traumatic stress disorders and social phobia; dementia of the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type; and adjustment disorder with depressed mood. Major depressive disorders may also result from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, etc.

Compounds of the invention are useful as analgesics. In particular they are useful in the treatment of traumatic pain such as postoperative pain; traumatic avulsion pain such as brachial plexus; chronic pain such as arthritic pain such as occurring in osteo-, rheumatoid or psoriatic arthritis; neuropathic pain such as post-herpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia, fibromyalgia, causalgia, peripheral neuropathy, diabetic neuropathy, chemotherapy-induced neuropathy, AIDS related neuropathy, occipital neuralgia, geniculate neuralgia, glossopharyngeal neuralgia, reflex sympathetic dystrophy, phantom limb pain; various forms of headache such as migraine, acute or chronic tension headache, temporomandibular pain, maxillary sinus pain, cluster headache; odontalgia; cancer pain; pain of visceral origin; gastrointestinal pain; nerve entrapment pain; sport's injury pain; dysmennorrhoea; menstrual pain; meningitis; arachnoiditis;musculoskeletal pain; low back pain e.g. spinal stenosis; prolapsed disc; sciatica; angina; ankylosing spondyolitis; gout; burns; scar pain; itch; and thalamic pain such as post stroke thalamic pain.

Compounds of the invention are also useful in the treatment of sleep disorders including dysomnia, insomnia, sleep apnea, narcolepsy, and circadian ritmic disorders.

Compounds of the invention are also useful in the treatment or prevention of the cognitive disorders. Cognitive disorders include dementia, amnestic disorders and cognitive disorders not otherwise specified.

Furthermore compounds of the invention are also useful as memory and/or cognition enhancers in healthy humans with no cognitive and/or memory deficit.

Compounds of the invention are also useful in the treatment of tolerance to and dependence on a number of substances. For example, they are useful in the treatment of dependence on nicotine, alcohol, caffeine, phencyclidine (phencyclidine like compounds), or in the treatment of tolerance to and dependence on opiates (e.g cannabis, heroin, morphine) or benzodiazepines; in the treatment of cocaine, sedative ipnotic, amphetamine or amphetamine-related drugs (e.g dextroamphetamine, methylamphetamine) addiction or a combination thereof.

Compounds of the invention are also useful as anti-inflammatory agents. In particular they are useful in the treatment of inflammation in asthma, influenza, chronic bronchitis and rheumatoid arthritis; in the treatment of inflammatory diseases of the gastrointestinal tract such as Crohn's disease, ulcerative colitis, inflammatory bowel disease and non-steroidal anti-inflammatory drug induced damage; inflammatory diseases of the skin such as herpes and eczema; inflammatory diseases of the bladder such as cystitis and urge incontinence; and eye and dental inflammation.

Compounds of the invention are also useful in the treatment of allergic disorders, in particular allergic disorders of the skin such as urticaria, and allergic disorders of the airways such as rhinitis.

Compounds of the invention are also useful in the treatment of emesis, i.e. nausea, retching and vomiting. Emesis includes acute emesis, delayed emesis and anticipatory emesis. The compounds of the invention are useful in the treatment of emesis however induced. For example, emesis may be induced by drugs such as cancer chemotherapeutic agents such as alkylating agents, e.g. cyclophosphamide, carmustine, lomustine and chlorambucil; cytotoxic antibiotics, e.g. dactinomycin, doxorubicin, mitomycin-C and bleomycin; anti-metabolites, e.g. cytarabine, methotrexate and 5- fluorouracil; vinca alkaloids, e.g. etoposide, vinblastine and vincristine; and others such as cisplatin, dacarbazine, procarbazine and hydroxyurea; and combinations thereof; radiation sickness; radiation therapy, e.g. irradiation of the thorax or abdomen, such as in the treatment of cancer; poisons; toxins such as toxins caused by metabolic disorders or by infection, e.g. gastritis, or released during bacterial or viral gastrointestinal infection; pregnancy; vestibular disorders, such as motion sickness, vertigo, dizziness and Meniere's disease; post-operative sickness; gastrointestinal obstruction; reduced gastrointestinal motility; visceral pain, e.g. myocardial infarction or peritonitis; migraine; increased intercranial pressure; decreased intercranial pressure (e.g. altitude

sickness); opioid analgesics, such as morphine; and gastro-oesophageal reflux disease, acid indigestion, over-indulgence of food or drink, acid stomach, sour stomach, waterbrash/regurgitation, heartburn, such as episodic heartburn, nocturnal heartburn, and meal-induced heartburn and dyspepsia.

Compounds of the invention are also useful in the treatment of gastrointestinal disorders such as irritable bowel syndrome; skin disorders such as psoriasis, pruritis and sunburn; vasospastic diseases such as angina, vascular headache and Reynaud's disease; cerebral ischeamia such as cerebral vasospasm following subarachnoid haemorrhage; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders related to immune enhancement or suppression such as systemic lupus erythematosus and rheumatic diseases such as fibrositis; and cough.

Compounds of the invention are of particular use in the treatment of depressive states, in the treatment of anxiety and of panic disorders.
Depressive states include major depressive disorders including bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, dysthymic disorder with early or late onset and with or without atypical features, neurotic depression and social phobia; dementia of the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type.

Compounds of the invention may be administered in combination with other active substances such as 5HT3 antagonists, serotonin agonists, selective serotonin reuptake inhibitors (SSRI), noradrenaline re-uptake inhibitors (SNRI), tricyclic antidepressants or dopaminergic antidepressants.

Suitable 5HT3 antagonists which may be used in combination of the compounds of the inventions include for example ondansetron, granisetron, metoclopramide.

Suitable serotonin agonists which may be used in combination with the compounds of the invention include sumatriptan, rauwolscine, yohimbine, metoclopramide.

Suitable SSRI which may be used in combination with the compounds of the invention include fluoxetine, citalopram, femoxetine, fluvoxamine, paroxetine, indalpine, sertraline, zimeldine.

Suitable SNRI which may be used in combination with the compounds of the invention include venlafaxine and reboxetine.

Suitable tricyclic antidepressants which may be used in combination with a compound of the invention include imipramine, amitriptiline, chlomipramine and nortriptiline.

Suitable dopaminergic antidepressants which may be used in combination with a compound of the invention include bupropion and amineptine.

It will be appreciated that the compounds of the combination or composition may be administered simultaneously (either in the same or different pharmaceutical formulations) or sequentially.

The invention therefore provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in therapy, in particular in human medicine.

There is also provided as a further aspect of the invention the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the preparation of a medicament for use in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins.

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, in particular in the treatment of conditions mediated bytachykinins, including substance P and other neurokinins, comprising administration of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

It will be appreciated that reference to treatment is intended to includeprophylaxis as well as the alleviation of established symptoms. Compounds of formula (I) may be administered as the raw chemical but the active ingredient is preferably presented as a pharmaceutical formulation.

Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound of formula (I) or a pharmaceutically acceptable salt thereof and formulated for administration by any convenient route. Such compositions are preferably in a form adapted for use in medicine, in particular human medicine, and can conveniently be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients.

Thus compounds of formula (I) may be formulated for oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or

hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

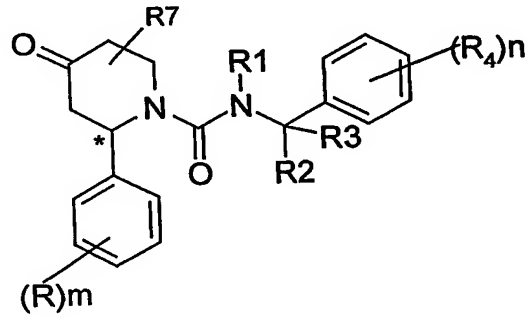
The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For intranasal administration, the compounds of the invention may be formulated as solutions for administration via a suitable metered or unitary dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

A proposed dose of the compounds of the invention is 1 to about 1000mg per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected.

Compounds of formula (I), and salts and solvates thereof, may be prepared by the general methods outlined hereinafter. In the following description, the groups R, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10}, m and n, have the meaning as previously defined for compounds of formula (I) unless otherwise stated.

According to one embodiment of the invention, a compound of formula (I) may be prepared by reductive N-alkylation of a compound of formula (II),

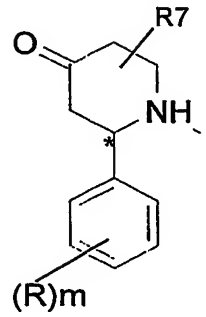


(II)

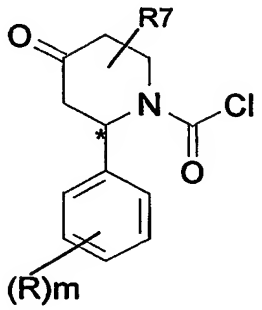
with amine (III) R_5R_6NH (III)

The reaction is suitable carried out in an aprotic solvent such as dichloroethane and in the presence of a suitable metal reducing agent such as sodium borohydride or sodium triacetoxyborohydride.

Compounds of formula (II) may be prepared by treating tetrahydro 4-pyridone compounds of formula (IV)

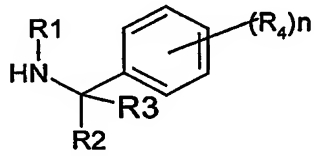


(IV)



(V)

with triphosgene in an aprotic solvent such as dichloromethane and in the presence of an organic base such triethylamine to form the intermediate carbonyl chloride compound (V) which may be isolated if required, followed by reaction of compound (V) with the amine compound (VI)



(VI)

The reaction conveniently takes place in an aprotic solvent such as a hydrocarbon, a halohydrocarbon such as dichloromethane or an ether such as tetrahydrofuran optionally in the presence of a base such as a tertiary amine e.g. diisopropylethylamine.

Where it is desired to isolate a compound formula (I) as a salt thereof, for example a pharmaceutically acceptable salt, this may be achieved by reacting the compound of formula (I) in the form of the free base with an appropriate amount of suitable acid and in a suitable solvent such as an alcohol (e.g. ethanol or methanol), an ester (e.g. ethyl acetate) or an ether (e.g. diethyl ether or tetrahydrofuran).

Pharmaceutically acceptable salts may also be prepared from other salts, including other pharmaceutically acceptable salts, of the compound of formula (I) using conventional methods.

Compounds of formula (III), (IV), (V) and (VI) may be prepared by analogous methods to those used for known compounds.

The compounds of formula (I) may readily be isolated in association with solvent molecules by crystallisation from or evaporation of an appropriate solvent to give the corresponding solvates.

When a specific enantiomer of a compound of general formula (I) is required, this may be obtained for example by resolution of a corresponding enantiomeric mixture of compounds of formula (I) using conventional methods.
Thus, for example, specific enantiomers of the compounds of formula (I) may be obtained from corresponding enantiomeric mixture of a compound of formula (I) using chiral HPLC procedure.

Alternatively, enantiomers of a compound of general formula (I) may be synthesised from the appropriate optically active intermediates using any of the general processes described herein.

Thus for example the required enantiomer may be prepared by the corresponding a chiral tetrahydro-4-pyridone of formula (III) using any of the processes described above for preparing compounds of formula (I) from compounds (III).

The chiral compounds (III) may be prepared from the corresponding racemic (III) using conventional procedures such as salt formation with a suitable optically active acid, separating the resultant diastereoisomeric salts by conventional means e.g chromatography and crystallisation followed by hydrolisis of the diastereoisomeric salts.
A suitable optically active acid for use in the process is L(+)mandelic acid.

In a further embodiment of the invention the enantiomers of the compound of formula (I) may be prepared by reaction of a chiral amine (V) using any of the process described above for preparing compounds of formula (I) from amine (V).
The chiral amine (III) may be prepared from the corresponding racemic amine (III) using any conventional procedures such as salt formation with a suitable optically active acid.

The invention is further illustrated by the following Intermediates and Examples which are not intended as a limitation of the invention.

In the Intermediates and Examples unless otherwise stated:

Melting points (m.p.) were determined on a Buchi m.p. apparatus and are uncorrected. All temperatures refer to 0°C.
Infrared spectra (IR) were measures in chloroform or nujol solutions on a FT-IR instrument.
Proton Magnetic Resonance (NMR) spectra were recorded either on Varian 400MHz or 500 MHz spectrometers as solutions in d_6-dimethylsulfoxide (d_6-DMSO), unless otherwise specified. Chemical shifts are recorded in ppm downfield using the residual solvent line as

internal reference. Splitting patterns are designed as s, singlet; d, double; t, triple; q, quartet; m, multiplet; b, broad. Mass spectra (MS) were taken on a VG Quattro mass spectrometer. Optical rotations were determined at 20°C with a Jasco DIP 360 Instrument (l=10 cm, cell volume= 1mL, λ=589 nm).

Flash silica gel chromatography was carried out over silica gel 230-400 mesh supplied by Merck AG Darmstadt, Germany. T.l.c. refers to thin layer chromatography on 0.25 mm silica gel plates (60F-254 Merck) and visualised with UV light.

Solutions were dried over anhydrous sodium sulphate.

Methylene chloride was redistilled over calcium hydride and tetrahydrofuran was redistilled over sodium.

The following abbreviation are used in the text: AcOEt = ethyl acetate, CH = cyclohexane; DCM = methylene chloride, DMF = N,N'-dimethylformamide, DIPEA = N,N-diisopropylethylamine, Et2O = diethyl ether, EtOH = ethanol, MeOH = methanol, TEA = triethylamine, THF = tetrahydrofuran.

Diastereoisomer A refers to a mixture of compounds having anti configuration as defined above.

Diastereoisomer B refers to a mixture of compounds having syn configuration as defined above.

Intermediate 1

1-(Benzyloxycarbonyl)-2-(4-fluoro-2-methyl-phenyl)-2,3-dihydro-4-pyridone

A small amount of iodine was added to a suspension of magnesium turnings (13.2 g) in dry THF (300 mL), at r.t., under a nitrogen atmosphere, then the mixture was vigorously refluxed for 20 minutes. To this suspension, a 15% of a solution of 2-bromo-5-fluoro-toluene (52.5 mL) in anhydrous THF (300 mL) was added. The suspension was heated under vigorous reflux until the brown colour disappeared. The remaining part of the bromide solution was added drop-wise over 1 hour to the refluxing suspension which was then stirred for a further 1 hour. This solution of Grignard reagent was then added drop-wise to the pyridinium salt obtained from benzyl chloroformate (48.7 mL) and 4-methoxypyridine (25 mL) in dry THF (900 mL) at -23°C.

The obtained solution was stirred 1 hour at -20°C then it was warmed up to 20°C, a 10% hydrochloric acid solution (560 mL) was added and the aqueous layer was extracted with AcOEt (2 x 750 mL).

The combined organic extracts were washed with 5% sodium hydrogen carbonate solution (600 mL) and brine (600 mL) then partially concentrated *in vacuo.*

CH (400 mL) was added drop-wise over 1 hour at 20°C and the resulting mixture was stirred 30 minutes and then filtered to give the title compound as a white solid (66 g).

IR (nujol): 1726 and 1655 (C=O), 1608(C=C) cm^{-1}.

NMR (d_6-DMSO): δ (ppm) 8.19 (d, 1H); 7.31-7.18 (m, 5H); 7.08 (m,2H); 6.94 (dt, 1H); 5.77 (d, 1H); 5.36 (d, 1H); 5.16 (2d, 2H); 3.26 (dd, 1H); 2.32 (d, 1H); 2.26 (s, 3H).

MS (ES/+): m/z=340 $[MH]^+$.

Intermediate 2

2-(4-Fluoro-2-methyl-phenyl)-piperidine-4-one

Method A

2-Methyl-4-fluoro-benzaldehyde (4 g) was added to a solution of 4-aminobutan-2-one ethylene acetal (3.8 g) in dry benzene (50 mL) and the solution was stirred at r.t. under a nitrogen atmosphere. After 1 hour the mixture was heated at reflux for 16 hours and then allowed to cool to r.t. This solution was slowly added to a refluxing solution of p-toluenesulphonic acid (10.6 g) in dry benzene (50 mL) previously refluxed for 1 hour with a Dean-Stark apparatus. After 3.5 hours the crude solution was cooled and made basic with a saturated potassium carbonate solution and taken up with AcOEt (50 mL). The aqueous phase was extracted with AcOEt (3 x 50 mL) and Et2O (2 x 50 mL). The organic layer was dried and concentrated *in vacuo* to a yellow thick oil as residue (7.23 g). A portion of the crude mixture (3 g) was dissolved in a 6N hydrochloric acid solution (20 mL) and stirred at 60°C for 16 hours. The solution was basified with solid potassium carbonate and extracted with DCM (5 x 50 mL). The combined organic phases were washed with brine (50 mL), dried and concentrated *in vacuo* to give the title compound (2.5 g) as a thick yellow oil.

Method B

L-selectride (1M solution in dry THF, 210 mL) was added drop-wise, over 80 minutes, to a solution of intermediate **1** (50 g) in dry THF (1065 mL) previously cooled to -72°C under a nitrogen atmosphere. After 45 minutes, 2% sodium hydrogen carbonate solution (994 mL) was added drop-wise and the solution was extracted with AcOEt (3 x 994 mL). The combined organic phases were washed with water (284 mL) and brine (568 mL). The organic phase was dried and concentrated *in vacuo* to get 1-benzyloxycarbonyl-2-(4-fluoro-2-methyl-phenyl)-piperidine-4-one as a pale yellow thick oil (94 g) which was used as a crude.

This material (94 g) was dissolved in AcOEt (710 mL), then 10% Pd/C (30.5 g) was added under a nitrogen atmosphere. The slurry was hydrogenated at 1 atmosphere for 30 minutes. The mixture was filtered through Celite and the organic phase was concentrated *in vacuo* to give the crude 2-(4-fluoro-2-methyl-phenyl)-piperidine-4-one as a yellow oil. This material was dissolved in AcOEt (518 mL) at r.t. and racemic camphorsulphonic acid (48.3 g) was added. The mixture was stirred at r.t for 18 hours, then the solid was filtered off, washed with AcOEt (2 x 50 mL) and dried *in vacuo* for 18 hours to give 2-(4-fluoro-2-methyl-phenyl)-piperidine-4-one, 10-camphorsulfonic acid salt as a pale yellow solid (68.5 g). (M.p.: 167-169°C - NMR (d_6-DMSO): □ (ppm) 9.43 (bs, 1H); 9.23 (bs, 1H); 7.66 (dd, 1H); 7.19 (m, 2H); 4.97 (bd, 1H); 3.6 (m, 2H); 2.87 (m, 3H); 2.66 (m, 1H); 2.53 (m, 2H); 2.37 (s + d, 4H); 2.22 (m, 1H); 1.93 (t, 1H); 1.8 (m, 2H); 1.26 (m, 2H); 1.03 (s, 3H); 0.73 (s, 3H).

This material (68.5 g) was suspended in AcOEt (480 mL) and stirred with a saturated sodium hydrogen carbonate (274 mL). The organic layer was separated and washed with further water (274 mL). The organic phase was dried and concentrated *in vacuo* to give the title compound (31 g) as a yellow-orange oil.

NMR (d_6-DMSO): δ (ppm) 7.49 (dd, 1H); 7.00 (m, 2H); 3.97 (dd, 1H); 3.27 (m, 1H); 2.82 (dt, 1H); 2.72 (bm, 1H); 2.47 (m, 1H); 2.40 (m, 1H); 2.29 (s, 3H); 2.25 (dt, 1H); 2.18 (m, 1H).

MS (ES/+): m/z=208 $[MH]^+$.

Intermediate 3

2-(4-Fluoro-2-methyl-phenyl)-4-oxo-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide.

A solution of triphosgene (1.43 g) dissolved in dry DCM (10 mL) was added to a solution of intermediate 2 (2.5 g) and DIPEA (8.4 mL) in dry DCM (20 mL) previously cooled to 0°C under a nitrogen atmosphere. The solution was stirred at 0°C for 2 hours, then (3,5-bis-trifluoromethyl-benzyl)-methylamine hydrochloride (5.63 g) and DIPEA (3.34 mL) were added. The mixture was stirred under nitrogen at r. t. for 14 hours. The mixture was taken up with AcOEt (50 mL), washed with cold 1N hydrochloric acid solution (3 x 20 mL) and brine (10 mL). The organic layer was dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (AcOEt/CH 3:7) to give the title compound as a white foam (3.85 g).

IR (nujol): 1721 and 1641 (C=O) cm^{-1}.

NMR (d_6-DMSO): δ (ppm) 7.96 (s, 1H); 7.76 (s, 2H); 7.25 (dd, 1H); 6.97 (dd, 1H); 6.90 (dt, 1H); 5.22 (t, 1H); 4.59 (d, 1H); 4.43 (d, 1H); 3.63-3.49 (m, 2H); 2.79 (s, 3H); 2.69 (m, 2H); 2.49 (m, 2H); 2.26 (s, 3H).

MS (ES/+): m/z = 491 $[MH]^+$.

Intermediate 4

2-(4-Fluoro-2-methyl-phenyl)-4-oxo-piperidine-1-carboxylic acid, [1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide (4a and 4b)

2-(R)-(4-Fluoro-2-methyl-phenyl)-4-oxo-piperidine-1-carboxylic acid, [1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide (4a) and

2-(S)-(4-Fluoro-2-methyl-phenyl)-4-oxo-piperidine-1-carboxylic acid, [1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide (4b)

Method A

A solution of triphosgene (147 mg) dissolved in dry DCM (5 mL) was added drop-wise to a solution of intermediate 2 (250 mg) and DIPEA (860 µL) in dry DCM (15 mL) previously cooled to 0°C under a nitrogen atmosphere. After 2 hours, [1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamine hydrochloride (503 mg) and DIPEA (320 µL) in dry acetonitrile (20 mL) were added and the mixture was heated to 70°C for 16 hours. Further [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamine hydrochloride (170 mg) and DIPEA (100 µL) were added and the mixture was stirred at 70°C for further 4 hours. Next, the mixture was allowed to cool to r.t., taken up with AcOEt (30 mL), washed with a 1N hydrochloric acid cold solution (3 x 15 mL) and brine (2 x 10 mL). The organic layer was dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (CH/AcOEt 8:2) to give:

1. intermediate **4a** (230 mg) as a white foam,
2. intermediate **4b** (231 mg) as a white foam.

Intermediate 4a:

NMR (d_6-DMSO): δ (ppm) 7.98 (bs, 1H); 7.77 (bs, 2H); 7.24 (dd, 1H); 6.97 (dd, 1H); 6.89 (m, 1H); 5.24 (t, 1H); 5.14 (q, 1H); 3.61 (m, 1H); 3.55 (m, 1H); 2.71 (m, 2H); 2.56 (s, 3H); 2.50 (m, 2H); 2.26 (s, 3H); 1.57 (d, 3H).
MS (ES/+): m/z = 505 $[MH]^+$.

Intermediate 4b:
NMR (d_6-DMSO): δ (ppm) 7.96 (bs, 1H); 7.75 (bs, 2H); 7.24 (dd, 1H); 6.98 (dd, 1H); 6.93 (dt, 1H); 5.29 (q, 1H); 5.24 (t, 1H); 3.56 (m, 1H); 3.48 (m, 1H); 2.70 (s, 3H); 2.50 (m, 4H); 2.26 (s, 3H); 1.54 (d, 3H).
MS (ES/+): m/z = 505 $[MH]^+$.

Intermediate 4a

Method B

A saturated sodium hydrogen carbonate solution (324 mL) was added to a solution of intermediate 9 (21.6 g) in AcOEt (324 mL) and the resulting mixture was vigorously stirred for 15 minutes. The aqueous layer was back-extracted with further AcOEt (216 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give intermediate **8** as a yellow oil, which was treated with TEA (19 mL) and AcOEt (114 mL). The solution obtained was added drop-wise over 40 minutes to a solution of triphosgene (8 g) in AcOEt (64 mL) previously cooled to 0°C under a nitrogen atmosphere, maintaining the temperature between 0°C and 8°C.
After stirring for 1 hours at 0°C and for 3 hours at 20°C, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamine hydrochloride (29.7 g), AcOEt (190 mL) and TEA (38 mL) were added to the reaction mixture which was then heated to reflux for 16 hours.
The solution was washed with 10% sodium hydroxide solution (180 mL), 1% hydrochloric acid solution (4 x 150 mL), water (3 x 180 mL) and brine (180 mL). The organic layer was dried and concentrated *in vacuo* to a residue, which was purified through a silica pad (CH/AcOEt 9:1) to give the title compound (21.5 g) as a brown thick oil.
NMR (d_6-DMSO): δ (ppm) 7.97-7.77 (bs + bs, 3H); 7.24 (dd, 1H); 6.97 (dd, 1H); 6.88 (td, 1H); 5.24 (m, 1H); 5.14 (q, 1H); 3.58 (m, 2H); 2.7 (m, 2H); 2.56 (s, 3H); 2.49 (m, 2H); 2.26 (s, 3H); 1.57 (d, 3H).

Intermediate 5
2-(S)-(4-Fluoro-2-methyl-phenyl)-4-oxo-piperidine-1-carboxylic acid, [1-(S)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide (5a) and
2-(R)-(4-Fluoro-2-methyl-phenyl)-4-oxo-piperidine-1-carboxylic acid, [1-(S)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide (5b)

A solution of triphosgene (147 mg) dissolved in dry DCM (5 mL) was added to a solution of intermediate **2** (250 mg) and DIPEA (860 µL) in dry DCM (15 mL) previously cooled to 0°C under a nitrogen atmosphere. After 2 hours, a solution of [1-(S)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamine hydrochloride (510 mg) and DIPEA (320 µL) in dry acetonitrile (20 mL) was added and the mixture was heated to 70°C for 16 hours. Next, further [1-(S)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamine hydrochloride (170 mg) and DIPEA (105 µL) were added. After further 4 hours at 70°C, the mixture was allowed to cool to r.t.,

taken up with AcOEt (30 mL), washed with a 1N hydrochloric acid cold solution (3 x 15 mL) and brine (2 x 10 mL). The organic layer was dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (CH/AcOEt 8:2) to give:

1. intermediate **5a** (234 mg) as a white foam,
2. intermediate **5b** (244 mg) as a white foam.

Intermediate 5a :

NMR (d_6-DMSO): δ (ppm) 7.98 (bs, 1H); 7.77 (bs, 2H); 7.24 (dd, 1H); 6.97 (dd, 1H); 6.89 (m, 1H); 5.24 (t, 1H); 5.14 (q, 1H); 3.61 (m, 1H); 3.55 (m, 1H); 2.71 (m, 2H); 2.56 (s, 3H); 2.50 (m, 2H); 2.26 (s, 3H); 1.57 (d, 3H).

MS (ES/+): m/z = 505 $[MH]^+$.

Intermediate 5b:

NMR (d_6-DMSO): δ (ppm) 7.96 (bs, 1H); 7.75 (bs, 2H); 7.24 (dd, 1H); 6.98 (dd, 1H); 6.93 (dt, 1H); 5.29 (q, 1H); 5.24 (t, 1H); 3.56 (m, 1H); 3.48 (m, 1H); 2.70 (s, 3H); 2.50 (m, 4H); 2.26 (s, 3H); 1.54 (d, 3H).

MS (ES/+): m/z = 505 $[MH]^+$.

Intermediate 6

2-(S)-(4-Fluoro-2-methyl-phenyl)-4-oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid, (1R, 2S, 5R)-2-isopropyl-5-methyl-cyclohexyl ester (6a) and

2-(R)-(4-Fluoro-2-methyl-phenyl)-4-oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid, (1R, 2S, 5R)-2-isopropyl-5-methyl-cyclohexyl ester (6b)

A solution of 2-bromo-5-fluoro-toluene (3.68 g) in dry THF (10 mL) was dropped over 30 minutes, into a mixture of magnesium (525 mg) and iodine (1 crystal) in dry THF (5 mL) previously heated to 70°C under a nitrogen atmosphere. The mixture was stirred at 70°C for 1.5 hours, then allowed to cool to r.t..

A solution of (-)-mentyl chloroformate (3.53 mL) in dry THF (15 mL) was added to a solution of 4-methoxypyridine (1.52 mL) in dry THF (35 mL) previously cooled to –78°C under a nitrogen atmosphere. After 15 minutes, the solution containing the 4-fluoro-2-methyl-phenyl magnesium bromide was added drop-wise, and the mixture was stirred at –78°C for 1 hour. The reaction was quenched by the addition of 1M hydrochloric acid solution (20 mL), warmed to r.t. and stirred at 23°C for 30 minutes. After extraction with AcOEt (2 x 150 mL), the combined organic extracts were washed with brine (50 mL), dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (CH/THF/toluene 8:1:1) to give:

1. intermediate **6a** (3.44g - yellow oil)
2. intermediate **6b** (530 mg- white solid).

Intermediate 6a:

T.l.c.: cyclohexane/THF/toluene 7:2:1, Rf=0.59.

IR (nujol): 1718 and 1675 (C=O) cm^{-1}.

NMR (d_6-DMSO): δ (ppm) 8.14 (d, 1H); 7.08 (dd, 1H); 7.02 (dd, 1H); 6.95 (m, 1H); 5.68 (d, 1H); 5.34(d, 1H); 4.47 (m, 1H); 3.26 (dd, 1H); 2.30 (m, 4H); 1.7 (m, 4H); 1.33 (m, 2H); 0.8 (m, 11H).

MS (ES/+): m/z=388 $[MH]^+$.

Intermediate 6b:

M.p.: 117-120°C.

T.l.c.: cyclohexane/THF/toluene 7:2:1, Rf=0.56.

IR (nujol): 1718 and 1669 (C=O) cm^{-1}.

NMR (d_6-DMSO): δ (ppm) 8.17 (d, 1H); 7.04-6.94 (m, 3H); 5.70 (d, 1H); 5.35 (d, 1H); 4.42 (m, 1H); 3.26 (dd, 1H); 2.30 (m, 4H); 1.58-1.40 (m, 3H); 1.2-0.7 (m, 8H); 0.51-0.34 (bs, 6H):

MS (ES/+): m/z=388 $[MH]^+$.

Intermediate 7

2-(R)-(4-Fluoro-2-methyl-phenyl)-2,3-dihydro-1H-pyridin-4-one

Sodium methoxide (100 mg) was added to a solution of intermediate **6b** (170 mg) in MeOH (15 mL) under a nitrogen atmosphere. The mixture was refluxed for two hours, and the solvent was removed *in vacuo*. The residue was partitioned between water (10 mL) and AcOEt (15 mL). The layers were separated, and the aqueous phase was extracted with further AcOEt (4 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried and concentrated *in vacuo* to give the title compound (145 mg) as a light yellow oil.

NMR (d_6-DMSO): δ (ppm) 7.71 (bd, 1H); 7.45 (dd, 1H); 7.38 (t, 1H); 7.03 (m, 2H); 4.86 (dd, 1H); 4.77 (d, 1H); 2.42 (dd, 1H); 2.31 (m, 4H)

MS (ES/+): m/z=206 $[M+H]^+$.

Intermediate 8

2-(R)-(4-Fluoro-2-methyl-phenyl)-piperidin-4-one

Palladium over charcoal (10% - 74 mg) was added to a solution of intermediate7 (145 mg) in MeOH (8 mL) and THF (2 mL). The mixture was allowed to react with hydrogen in a pressure reactor (2 atm) overnight. After flushing with nitrogen, the solution was filtered and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (AcOEt/MeOH 9:1) to give the title compound (26 mg) as a yellow oil.

The enantiomeric excess (90-95%) was detected by chiral HPLC.

T.l.c.:AcOEt/MeOH 9:1, Rf=0.2.

NMR (d_6-DMSO): δ (ppm) 7.49 (dd, 1H); 7.00 (m, 2H); 3.97 (dd, 1H); 3.27 (m, 1H); 2.82 (dt, 1H); 2.72 (bm, 1H); 2.47 (m, 1H); 2.40 (m, 1H); 2.29 (s, 3H); 2.25 (dt, 1H); 2.18 (m, 1H).

MS (ES/+): m/z=208 $[MH]^+$.

Intermediate 9

2-(R)-(4-Fluoro-2-methyl-phenyl)-piperidin-4-one L-(+)-mandelate.

A solution of L-(+)-mandelic acid (22.6 g) in AcOEt (308 mL) was added to a solution of intermediate 2 (31 g) in AcOEt (308 mL). Then isopropanol (616 mL) was added and the solution was concentrated *in vacuo* to 274 mL. The solution was then cooled to 0°C and further cold isopropanol (96 mL) was added. The thick precipitate was stirred under nitrogen

for 5 hours at 0°C, then filtered and washed with cold Et2O (250 mL) to give the title compound as a pale yellow solid (20.3 g).
M.p.: 82-85°C.
NMR (d_6-DMSO): δ (ppm) 7.51 (dd, 1H); 7.40 (m, 2H); 7.32 (m, 2H); 7.26 (m, 1H); 7.0 (m, 2H); 4.95 (s, 1H); 4.04 (dd, 1H); 3.31 (m, 1H); 2.88 (m, 1H); 2.49-2.2 (m, 4H); 2.29 (s, 3H).
Chiral HPLC: HP 1100 HPLC system; column Chiralcel OD-H, 25 cm x 4.6 mm; mobile phase: n-hexane/isopropanol 95:5 + 1% diethylamine; flow: 1.3 ml/min; detection: 240/215nm; retention time 12.07 minutes.

Intermediate 10
2-(R)-4-Fluoro-2-methyl-phenyl)-4-oxo-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide
Method A
A solution of triphosgene (17 mg) in dry DCM (2 mL) was added to a solution of intermediate **8** (26 mg) and DIPEA (65 mg) in dry DCM (3 mL) previously cooled to 0°C under a nitrogen atmosphere. After two hours acetonitrile (10 mL) was added, the temperature was allowed to reach r.t. and the DCM evaporated under a nitrogen flush. Then, a solution of 3,5-(bis-trifluoromethyl-benzyl)-methylamine hydrochloride (74 mg) and DIPEA (130 mg) in acetonitrile (3 mL) was added and the mixture was stirred at 23°C overnight. The solvent was concentrated *in vacuo*. The residue was dissolved in AcOEt (10 mL) and washed with 1N hydrochloric acid solution (3 x 5 mL), 5% sodium hydrogen carbonate (5 mL) and brine (10 mL). The organic layer was dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (CH/AcOEt 1:1) to give the title compound (50 mg) as a white solid.
Method B
A saturated sodium hydrogen carbonate solution (348 mL) was added to a solution of intermediate **9** (23.2 g) in AcOEt (348 mL) and the resulting mixture was vigorously stirred for 15 minutes. The aqueous layer was back-extracted with further AcOEt (230 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give intermediate **8** (12.31 g) as a yellow oil, which was treated with TEA (20.5 mL) and AcOEt (123 mL). The solution obtained was added drop-wise over 40 minutes to a solution of triphosgene (8 g) in AcOEt (61 mL) previously cooled to 0°C under a nitrogen atmosphere, maintaining the temperature between 0°C and 8°C.
After stirring for 2 hours at 20°C, 3,5-(bis-trifluoromethyl-benzyl)-methylamine hydrochloride (28.1 g), AcOEt (184 mL) and TEA (33 mL) were added to the reaction mixture which was then further stirred for 2 hours at 20°C.
The solution was washed with 10% sodium hydroxide solution (3 x 185 mL) and 1% hydrochloric acid solution (3 x 185 mL). The organic layer was dried and concentrated *in vacuo* to a crude (38 g), which was purified through a silica pad (CH/AcOEt from 9:1 to 1:1) to give the title compound (24.7 g) as a colourless oil.

NMR (d_6-DMSO): δ (ppm) 7.96 (s, 1H); 7.76 (s, 2H); 7.26 (dd, 1H); 6.98 (dd, 1H); 6.90 (td, 1H); 5.23 (t, 1H); 4.61 (d,1H); 4.41 (d, 1H); 3.60 (m, 2H); 2.69 (m,2H); 2.79 (s, 3H); 2.50 (m, 2H); 2.27 (s,3H).
MS (ES/+): m/z=491 $[MH]^+$.

Intermediate 11
2-(4-Fluoro-2-methyl-phenyl)-4-hydroxy-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide

A solution of intermediate 3 (150 mg) and sodium borohydride (13 mg) in dry MeOH (5 mL) was stirred at 0°C for 2 hours under a nitrogen atmosphere. The crude solution was washed with a saturated ammonium chloride solution (4 mL) and taken up with AcOEt (5 mL). The aqueous phase was extracted with AcOEt (3 x 5 mL) and the combined organic phases were washed with brine (5 mL). The organic layer was dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (AcOEt/CH 7:3) to give:

1. intermediate **11a** (4 mg)
2. intermediate **11b** (30 mg).

Intermediate 11a (diastereoisomer A)
NMR (d_6-DMSO): δ (ppm) 7.94 (bs, 1H); 7.63 (bs, 2H); 7.22 (bs, 1H); 6.88 (dd, 1H); 6.77 (dt, 1H); 4.69 (d, 1H); 4.60 (d, 1H); 4.36 (d, 1H); 4.13 (dd, 1H); 3.94 (m, 1H); 3.57 (m, 1H); 2.88 (s, 3H); 2.65 (m, 1H); 2.48 (s, 3H); 1.83 (m, 1H); 1.62 (m, 2H); 1.22 (m, 1H).
MS (ES/+): m/z = 493 $[MH]^+$, 475 $[M\text{-}OH]^+$

Intermediate 11b (diastereoisomer B)
NMR (d_6-DMSO): δ (ppm) 7.93 (bs, 1H); 7.58 (bs, 2H); 7.21 (dd, 1H); 6.88 (dd, 1H); 6.77 (dt, 1H); 4.78 (d 1H); 4.62 (d, 1H); 4.33 (d, 1H); 4.13 (dd, 1H); 3.58 (m, 1H); 3.37 (m, 1H); 2.90 (s, 3H); 2.67 (m, 1H); 2.32 (s, 3H); 1.89 (m, 1H); 1.83 (m, 1H); 1.52 (dq, 1H); 1.29 (q, 1H).
MS (ES/+): m/z = 493 $[MH]^+$, 475 $[M\text{-}OH]^+$.

Example 1
4-(R,S)-(2,2,2-Trifluoroethyl)-amino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride .

A solution of intermediate **4a** (120 mg), 2,2,2-trifluoroethylamine (190 µL) in dry 1,2-dichloroethane (10 mL) was stirred at 23°C for 1 hours under a nitrogen atmosphere, then sodium triacetoxyborohydride (75.7 mg) was added. The mixture was stirred at 23°C for 18 hours, then further 2,2,2-trifluoroethylamine (190 µL) and few drops of acetic acid were added and the solution was stirred for further 24 hours. The solution was washed with a 5% sodium hydrogen carbonate solution (10 mL) and brine (10 mL). The organic layer was dried and concentrated *in vacuo* to a residue that was purified by flash chromatography (CH/AcOEt 6:4) to give the 4-(2,2,2-trifluoroethyl)amino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide (27 mg - T.l.c.: CH/AcOEt 1:1 Rf=0.77) as an enantiomeric mixture in ratio C-2 and C-4 anti/syn 4:6.

This material (25 mg) was dissolved in dry Et2O (5 mL) and treated with hydrochloric acid (1M in Et2O – 1 mL). The resulting mixture was stirred at 23°C for 30 minutes, then concentrated *in vacuo* to give the title compound as a whitish solid (25 mg).
M.p.: 116-7°C
IR (nujol): 1659 and 1651 (C=O) cm^{-1}.
NMR (d_6-DMSO): δ (ppm) 7.91 (s, 1H); 7.73 (s, 1H); 7.68 (s, 1H); 7.23 and 7.17 (2dd, 1H); 6.74-6.76 (m, 2H); 5.3 and 5.18 (2q, 1H); 4.9 and 4.18 (m and dd, 1H); 3.5-3.1 (m, 3H); 2.74 and 2.65 (2s, 3H); 2.35 and 2.28 (2s, 3H); 2.1-1.5 (m, 4H); 1.5 and 1.46 (2d, 3H).
MS (ES/+): m/z=588 $[MH-HCl]^+$.

Example 2

4-(R)-(2,2-Dimethyl-propylamino)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride (2a)

4-(S)-(2,2-Dimethyl-propylamino)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride (2b)

A solution of intermediate 4a (120 mg), 2,2-dimethyl-propylamine (20.9 mg) and sodium triacetoxyborohydride (78.2 mg) in dry 1,2-dichloroethane (5 mL) was stirred at 23°C for 2 hours under a nitrogen atmosphere. The solution was washed with a 5% sodium hydrogen carbonate solution (10 mL) and brine (10 mL). The organic layer was dried and concentrated *in vacuo* to a residue that was purified by flash chromatography (AcOEt/MeOH 85:15) to give three fractions:

1. diastereoisomer 1 (65.4 mg - T.l.c.: AcOEt/MeOH 7:3 Rf=0.41),
2. a mixture of the two diastereoisomers (15.0 mg)
3. diastereoisomer 2 (22.0 mg - T.l.c.: AcOEt/MeOH 7:3 Rf=0.39).

Example 2a

A solution of diastereoisomer 1 (64.0 mg) in Et2O (5 mL) was treated with hydrochloric acid (1M in Et2O – 1 mL). The resulting solution was stirred at 23°C for 30 minutes, then it was concentrated *in vacuo* to give the title compound as a white solid (67.4 mg).
IR (nujol): 3376 (NH_2^+), 1627 (C=O) cm^{-1}.
NMR (d_6-DMSO): δ (ppm) 8.16,8.10 (2bm, 2H); 7.99 (s, 1H); 7.78 (s, 2H); 7.39 (dd, 1H); 7.00 (dd, 1H); 6.93 (dt, 1H); 5.24 (t, 1H); 5.09 (q, 1H); 3.54 (m, 2H); 3.05 (t, 1H); 2.81 (m, 2H); 2.60 (s, 3H); 2.31 (m, 1H); 2.20 (s, 3H); 2.13 (m, 2H); 1.57 (d, 3H); 1.62 (m, 1H); 0.98 (s, 9H).
MS (ES/+): m/z=576 $[MH-HCl]^+$.

Example 2b

A solution of diastereoisomer 2 (21.0 mg) in dry diethyl ether (5 mL) was treated with hydrochloric acid (1M in diethyl ether – 1 mL). The resulting mixture was stirred at 23°C for 15 minutes, then filtered and further treated with dry diethyl ether to give thetitle compound as a whitish solid (11 mg).

NMR (d_6-DMSO): δ (ppm) 7.99 (bs, 3H); 7.67 (bs, 1H); 7.16 (m, 1H); 6.96 (m, 1H); 6.95 (m, 1H); 5.29 (m, 1H); 4.20 (m, 1H); 3.5-2.7 (m, 5H); 2.62 (s, 3H); 2.35 (s, 3H); 2.7-2.0 (m, 4H); 1.45 (d, 3H); 0.95 (s, 9H).
MS (ES/+): m/z=576 $[MH\text{-}HCl]^+$.

Example 3

4-(R)-Ethylamino-2-(R)-4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride (3a)

4-(S)-Ethylamino-2-(R)-4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride (3b)

A suspension of intermediate 4a (100 mg), ethylamine hydrochloride (326 mg), triethylamine (613 μL) and sodium triacetoxyborohydride (63 mg) in dry 1,2-dichloroethane (2.5 mL) was stirred at 23°C for 6 hours under a nitrogen atmosphere. The solution was diluted with DCM (10 ml) washed with a 5% sodium hydrogen carbonate solution (10 mL) and brine (10 mL). The organic layer was dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (AcOEt/MeOH 9:1) to give two fractions:

1. diastereoisomer 1 (50 mg – T.l.c. AcOEt/MeOH 8:2 Rf=0.2)
2. diastereoisomer 2 (10 mg – T.l.c. AcOEt/MeOH 8:2 Rf=0.13)

Example 3a

A solution of diastereoisomer 1 (50 mg) in dry Et2O (5 mL) was treated with hydrochloric acid (1M in Et2O – 2 mL) and the resulting solution was stirred at 23°C for 30 minutes, then it was concentrated *in vacuo*. The residue was triturated with Et2O to give the title compound as a white solid (24 mg).
NMR (d_6-DMSO): □ (ppm) 8.56 (bs, 2H); 7.99 (s, 1H); 7.75 (s, 2H); 7.32 (dd, 1H); 6.98 (dd, 1H); 6.90 (m, 1H); 5.12 (q, 1H); 5.04 (t, 1H); 3.6-3.4 (m, 2H); 3.13 (t, 1H); 2.97 (m, 2H); 2.61 (s, 3H); 2.25 (s, 3H); 2.10 (m, 2H); 1.98 (m, 1H); 1.65 (m, 1H); 1.55 (d, 3H); 1.19 (t, 3H).
MS (ES/+): m/z=534 $[MH\text{-}HCl]^+$.

Example 3b

A solution of diastereoisomer 2 (10 mg) in dry Et2O (2 mL) was treated with hydrochloric acid (1M in Et2O – 0.5 mL). The resulting mixture was stirred at 23°C for 30 minutes, then it was concentrated *in vacuo*. The residue was triturated with Et2O to give the title compound as a white solid (7 mg).
NMR (d_6-DMSO): □ (ppm) 8.60 (bs, 2H); 7.99 (s, 1H); 7.67 (s, 2H); 7.15 (dd, 1H); 6.94 (dd, 1H); 6.83 (dt, 1H); 5.29 (q, 1H); 4.19 (dd, 1H); 3.43 (bd, 1H); 3.30 (m, 1H); 2.97 (bm, 2H); 2.80 (t, 1H); 2.74 (s, 3H); 2.35 (s, 3H); 2.11 (bd, 1H); 2.06 (bd, 1H); 1.68 (m, 1H); 1.57 (m, 1H); 1.45 (d, 3H); 1.17 (t, 3H).
MS (ES/+): m/z=534 $[MH\text{-}HCl]^+$.

Example 4

4-(R)-Dimethylamino-2-(R)-4-(fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride (4a)

4-(S)-Dimethylamino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride (4a)

A solution of intermediate **4a** (93 mg), dimethylamine (2 M in THF - 40 □L) and sodium triacetoxyborohydride (57 mg) in dry 1,2-dichloroethane (10 mL) was stirred at 23°C for 6 hours under a nitrogen atmosphere. The solution was washed with a 5% sodium hydrogen carbonate solution (10 mL) and brine (10 mL). The organic layer was dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (AcOEt/MeOH 95:5 to 80:20) to give two fractions:

1. diastereoisomer 1 (39 mg - T.l.c.: AcOEt/MeOH 8:2 Rf=0.2),
2. diastereoisomer 2 (26 mg - T.l.c.: AcOEt/MeOH 8:2 Rf=0.15).

Example 4a

A solution of diastereoisomer 1 (39 mg) in dry Et2O (5 mL) was treated with hydrochloric acid (1M in Et2O – 2 mL) and the resulting solution was stirred at 23°C for 5 minutes. The solution was concentrated *in vacuo* to give a white solid that was triturated in Et2O (2 mL), then filtered to give the title compound as a white solid (16 mg).

IR (nujol): 3443 (NH_2^+), 1640 (C=O) cm^{-1}.

NMR (d_6-DMSO): δ (ppm) 9.64 (bs, 1H); 7.99 (s, 1H); 7.76 (s, 2H); 7.35 (dd, 1H); 7.00 (dd, 1H); 6.92 (bt, 1H); 5.19 (bt, 1H); 5.07 (q, 1H); 3.58 (m, 1H); 3.17 (t, 1H); 2.77 (bs, 3H); 2.73 (bs, 3H); 2.55 (s, 3H); 2.21 (s + m, 3H +1H); 2.07 (bm, 2H); 1.63 (dq, 1H); 1.55 (d, 3H).

MS (ES/+): m/z=534 $[MH\text{-}HCl]^+$.

Example 4b

A solution of diastereoisomer 2 (26 mg) in dry Et2O (5 mL) was treated with hydrochloric acid (1M in Et2O – 2 mL) and the resulting solution was stirred at 23°C for 5 minutes. The solution was concentrated *in vacuo* to give a white solid that was triturated in Et2O (2 mL), then filtered to give the title compound as a white solid (24 mg).

IR (nujol): 3399 (NH_2^+), 1665 (C=O) cm^{-1}.

NMR (d_6-DMSO): δ (ppm) 9.75 (bs, 1H); 7.99 (s, 1H); 7.67 (s, 2H); 7.22 (dd, 1H); 6.93 (dd, 1H); 6.81 (dt, 1H); 5.31 (q, 1H); 4.17 (dd, 1H); 3.44 (m, 2H); 2.76 (t, 1H); 2.73 (s, 3H); 2.72 (s, 3H+3H); 2.35 (s, 3H); 2.08 (d, 1H); 2.01 (d, 1H); 1.85 (dq, 1H); 1.64 (q, 1H); 1.46 (d, 3H)

Example 5

4-(R)-Dimethylamino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide hydrochloride (5a)

4-(S)-Dimethylamino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide hydrochloride (5b)

A solution of intermediate **10** (1.0 g) and dimethylamine (2 M in THF) (50mL) in MeOH (40 mL) was stirred at 23°C for 5 hours, then a solution of sodium borohydride (85 mg) in dry MeOH (10 mL) was added. The resulting mixture was stirred at 23°C for 30 minutes, then a 5% solution of sodium hydrogen carbonate (20 mL) was added. The mixture was concentrated *in vacuo* to eliminate the alcohol, then the aqueous phase was extracted with AcOEt (3 x 50 mL). The combined organic extracts were dried and concentrated *in vacuo* to

a residue which was purified by flash chromatography (AcOEt/MeOH 7:3) to give three fractions:

1. diastereoisomer 1 (61 mg as a white solid T.l.c.: AcOEt/MeOH 8:2, Rf=0.23)
2. mixture of the two diastereoisomers (190 mg)
3. diastereosiomerr 2 (436 mg as a white solid - T.l.c.: AcOEt/MeOH 8:2, Rf=0.2).

Example 5a

A solution of diastereoisomer 1 (61 mg) in dry Et2O (5 mL) was treated with hydrochloric acid (1M in Et2O – 0.12 mL). The resulting mixture was stirred at 0°C for 15 minutes, then filtered to give the title compound as a white solid (55 mg).

M.p.: 180-3°C

NMR (d_6-DMSO): δ (ppm) 9.78 (bs, 1H); 7.97 (s, 1H); 7.79 (s, 2H); 7.35 (dd, 1H); 7.0 (dd, 1H); 6.92 (dt, 1H); 5.17 (bt, 1H); 4.56 (d, 1H); 4.41 (d, 1H); 3.56 (bm, 2H); 3.1 (t, 1H); 2.75 (m + s, 9H); 2.23 (s, 4H); 2.09 (bm, 2H); 1.66 (m, 1H).

MS (ES/+): m/z=520 $[M-Cl]^+$.

Example 5b

A solution of diastereoisomer 2 (436 mg) in dry Et2O (25 mL) was treated with hydrochloric acid (1M in Et2O – 0.85 mL). The resulting mixture was stirred at 0°C for 15 minutes, then filtered to give the title compound (380 mg) as a white solid.

M.p.: 147-150°C

IR (nujol): 3406 (NH_2^+), 1656 (C=O) cm^{-1}.

NMR (d_6-DMSO): δ (ppm) 9.87 (bs, 1H); 7.95 (s, 1H); 7.59 (s, 2H); 7.27 (dd, 1H); 6.94 (dd, 1H); 6.82 (m, 1H); 4.63 (d, 1H); 4.37 (d, 1H); 4.2 (dd, 1H); 3.54 (m, 1H); 3.3 (m, 1H); 2.92 (s, 3H); 2.70 (m, 6H); 2.70 (m, 1H); 2.36 (s, 3H); 2.1-2.00 (m, 2H); 1.85 (m, 1H); 1.6 (m, 1H).

MS (ES/+): m/z=520 $[M-Cl]^+$.

$[\lambda]_D$ = -82.77 (1.07% in DMSO).

Example 6

4-(R)-(2-Fluoroethyl)-amino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis)-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride (6a)

4-(S)-(2-Fluoroethyl)-amino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis)-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride (6b)

A suspension of intermediate 4a (100 mg), 2-fluoroethylamine hydrochloride (98 mg), TEA (100 µL) and sodium triacetoxyborohydride (65 mg) in dry 1,2-dichloroethane (8 mL) was stirred at 23°C for 2 hours under a nitrogen atmosphere. A further amount of 2-fluoroethylamine hydrochloride (98 mg) and TEA (100 µL) were added and the mixture stirred for 2 hours at 23°C. A further amount of sodium triacetoxyborohydride (65.0 mg) was added and the mixture stirred at 23°C for 1.5 hours under a nitrogen atmosphere.

The solution was washed with a saturated sodium hydrogen carbonate solution (8 mL) and brine (8 mL). The organic layer was dried and concentrated *in vacuo* to a residue that was purified by flash chromatography (AcOEt/MeOH 95:5) to give two fractions:

1. diastereoisomer 1 (26.0 mg - T.l.c.: AcOEt/MeOH 8:2 Rf=0.44)

2. diastereoisomer 2 (17.0 mg - T.l.c.: AcOEt/MeOH 8:2 Rf=0.3).

Example 6a

A solution of diastereoisomer 1 (26.0 mg) in dry Et2O (1 mL) was treated with hydrochloric acid (1M in Et2O – 20 µL), and the resulting solution was stirred at 0°C for 15 minutes. The solution was concentrated *in vacuo* and the residue was triturated with n-pentane (1 mL) to give the title compound as a white solid (21 mg).

NMR (d_6-DMSO): δ (ppm) 8.96 (bs, 2H); 7.99 (s, 1H); 7.75 (s, 2H); 7.34 (dd, 1H); 7.00 (dd, 1H); 6.91 (m, 1H); 5.16-5.06 (m, 2H); 4.84-4.6 (m, 2H); 3.64-3.10 (m, 5H); 2.3-1.65 (m, 4H); 2.60 (s, 3H); 2.24 (s, 3H); 1.55 (d, 3H).

MS (ES/+): m/z=552 $[MH\text{-}HCl]^+$.

Example 6b

A solution of diastereoisomer 2 (17.0 mg) in dry Et2O (1 mL) was treated with hydrochloric acid (1M in Et2O – 20 µL), and the resulting solution was stirred at 0°C for 15 minutes. The solution was concentrated *in vacuo* and the residue was triturated with n-pentane (1 mL) to give the title compound as a white solid (15 mg).

NMR (d_6-DMSO): δ (ppm) 8.93 (s, 2H); 7.99 (s, 1H); 7.67 (s, 2H); 7.15 (dd, 1H); 6.94 (dd, 1H); 6.83 (m, 1H); 5.28 (q, 1H); 4.8-4.6 (m, 2H); 4.18 (dd, 1H); 3.4 (m, 3H); 2.8-2.7 (m, 2H); 2.2-2.0 (m, 2H); 1.8-1.5 (m, 2H); 2.73 (s, 3H); 2.34 (s, 3H); 1.45 (d, 3H).

MS (ES/+): m/z=552 $[MH\text{-}HCl]^+$.

Example 7

4-(R)-(2-Fluoro-ethylamino)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide hydrochloride (7a)

4-(S)-(2-Fluoro-ethylamino)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide hydrochloride (7b)

A solution of intermediate **10** (65 mg), 2-fluoroethylamine hydrochloride (132 mg), TEA (184 µL) and sodium triacetoxyborohydride (42 mg) in dry acetonitrile (5 mL) was stirred at r.t. under a nitrogen atmosphere. After 6 hours further 2-fluoroethylamine hydrochloride (264 mg), TEA (368 µL) and sodium triacetoxyborohydride (15 mg) were added. After stirring at r.t. for 20 hours, the crude solution was quenched with a 5% sodium hydrogen carbonate solution (4 mL) and taken up with AcOEt (5 mL). The aqueous phase was extracted with AcOEt (3 x 5 mL) and the combined organic phases were washed with brine (5 mL). The organic layer was dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (AcOEt/MeOH 95:5) to give two fractions:

1. diastereoisomer 1 (35 mg – T.l.c. AcOEt/MeOH 9:1 Rf=0.4)
2. diastereoisomer 2 (32 mg - T.l.c. AcOEt/MeOH 9:1 Rf=0.27).

Example 7a:

A solution of diastereoisomer 1 (30 mg) in dry Et2O (5 mL) was treated with hydrochloric acid (1M in Et2O – 0.5 mL) at 0°C and the resulting solution was stirred under a nitrogen atmosphere for 30 minutes. The solution was concentrated *in vacuo* and the residue was triturated with diethyl ether to give the title compound as a whitish solid (26 mg).

M.p.: 145-6°C

IR (nujol): 3404 (NH_2^+), 1629 (C=O) cm^{-1}.
NMR (d_6-DMSO): δ (ppm) 9.04 (bs, 2H); 7.99 (s, 1H); 7.77 (s, 2H); 7.35 (dd, 1H); 6.99 (dd, 1H); 6.91 (dt, 1H); 5.09 (bt, 1H); 4.75 (bd, 2H); 4.58 (d, 1H); 4.43 (d, 1H); 3.64 (bm, 1H); 3.45-3.3 (m, 3H); 3.11 (dd, 1H); 2.81 (s, 3H); 2.27 (s, 3H); 2.17 (bm, 1H); 2.1 (bm, 2H); 1.69 (m, 1H).
MS (ES/+): m/z = 538 $[MH\text{-}HCl]^+$.

Example 7b

A solution of diastereoisomer 2 (32 mg) in dry Et2O (2 mL) was treated with hydrochloric acid (1M in Et2O – 70 μL) at 0°C and the resulting solution was stirred under a nitrogen atmosphere for 15 minutes. The solution was concentrated *in vacuo* and the residue was triturated from Et2O /n-pentane to give the title compound as a white solid (27 mg).
IR (nujol): 3410 (NH^+), 1660 (C=O) cm^{-1}.
NMR (d_6-DMSO): δ (ppm) 9.0-8.8 (bm, 2H); 7.95 (bs, 1H); 7.59 (bs, 2H); 7.20 (dd, 1H); 6.94 (dd, 1H); 6.84 (m 1H); 4.70 (bd, 2H); 4.63 (d, 1H); 4.33 (d, 1H); 4.20 (dd, 1H); 3.51 (m, 1H); 3.37 (bm, 3H); 2.93 (s, 3H); 2.75 (m, 1H); 2.35 (s, 3H); 2.16 (m, 1H); 2.11 (m, 1H); 1.73 (m, 1H); 1.54 (m, 1H).
MS (ES/+): m/z = 538 $[MH\text{-}HCl]^+$.

Example 8

4-(S)-(N-2-Fluoroethyl-N-methylamino)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide hydrochloride

Formaldehyde (37% in water – 43 μL), 10% palladium over charcoal (10 mg) and 1 drop of acetic acid were added to a solution of example **7b** (28 mg) in MeOH (1.5 mL). The mixture was stirred at r.t. under a hydrogen atmosphere for 1 hour, then it was filtered though celite and concentrated *in vacuo*. The residue was purified by flash chromatography (AcOEt/MeOH 9:1) to give the desired 4-(S)-(N-2-fluoroethyl-N-methylamino)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide (13 mg) as yellow gum. This material was dissolved in dry Et2O (2 mL), treated with hydrochloric acid (1M in Et2O – 0.5 mL) and the resulting solution was stirred under a nitrogen atmosphere for 15 minutes. The solution was concentrated *in vacuo* and the residue was triturated from Et2O /n-pentane to give the title compound as a white solid (11.6 mg).
M.p.: 80-81°C (dec)
T.l.c.: AcOEt/MeOH 8:2, Rf=0.37 (free base).
IR (nujol): 3387 (NH^+), 1653 (C=O) cm^{-1}.
NMR (d_6-DMSO): δ (ppm) 10.04 (bm, 1H); 7.96 (s, 1H); 7.6 (s, 2H); 7.28 (dd, 1H); 6.94 (dd, 1H); 6.83 (dt 1H); 4.84 (bd, 2H); 4.64 (d, 1H); 4.37 (d, 1H); 4.22 (bdd, 1H); 3.6 (bm, 2H); 3.54 (bd, 1H); 3.43 (m, 1H); 2.93 (s, 3H); 2.78 (m, 4H); 2.37 (s, 3H); 2.15-2.0 (m, 2H); 1.94 (dt, 1H); 1.65 (dq, 1H).
MS (ES/+): m/z = 552 $[MH\text{-}HCl]^+$.

Example 9

2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(R)-(2-methoxyethylamino)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride (9a)
2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-(2-methoxyethylamino)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride (9b)

A solution of intermediate **4a** (100 mg), 2-methoxyethylamine (17 µL) and sodium triacetoxyborohydride (65 mg) in dry 1,2-dichloroethane (5 mL) was stirred at 23°C for 2 hours under a nitrogen atmosphere. The solution was washed with a 5% sodium hydrogen carbonate solution (10 mL) and brine (10 mL). The organic layer was dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (AcOEt/MeOH 8:2) to give two fractions:

1. diastereoisomer 1 (C-2 and C-4 anti configuration - 40 mg)
2. diastereoisomer 2 (C-2 and C-4 syn configuration - 20 mg)

Example 9a

A solution of diastereoisomer 1 (40 mg) in dry Et2O (3 mL) was treated with hydrochloric acid (1M in Et2O – 0.5 mL) and the resulting solution was stirred at 0 C° for 5 minutes. The solution was concentrated *in vacuo* and the residue was triturated with n-pentane (2 mL) to give the title compound as a white solid (40 mg).
IR (nujol): 3396 (NH_2^+), 1640 (C=O) cm^{-1}.
NMR (d_6-DMSO): δ (ppm) 8.67-8.62 (bs, 2H); 7.99 (s, 1H); 7.76 (s, 2H); 7.34 (dd, 1H); 6.99 (dd, 1H); 6.91 (m, 1H); 5.12 (m, 1H); 5.09 (m, 1H); 3.6-3.4 (m, 4H); 3.16 (m, 3H); 2.25-1.60 (m, 4H); 3.3 (m, 3H); 2.59 (s, 3H); 2.23 (s, 3H); 1.55 (d, 3H);
MS (ES/+): m/z=564 $[M-Cl]^+$.

Example 9b

A solution of diastereoisomer 2 (20 mg) in dry Et2O (3 mL) was treated with hydrochloric acid (1M in Et2O – 0.5 mL). The resulting solution was stirred at 23 C° for 30 minutes, then it was concentrated *in vacuo*. The residue was triturated with n-pentane (2 mL) to give the title compound as a white solid (20 mg).
IR (nujol): 3421 (NH_2^+), 1656-1650 (C=O) cm^{-1}.
NMR (d_6-DMSO): δ (ppm) 8.64 (bs, 2H); 7.99 (s, 1H); 7.67 (s, 2H); 7.14 (dd, 1H); 6.94 (dd, 1H); 6.83 (m, 1H); 5.28 (q, 1H); 4.17 (dd, 1H); 3.55 (t, 2H); 3.42 (m, 1H); 3.13 (m, 2H); 2.8-2.7 (m, 2H); 2.2-1.5 (m, 4H); 3.3 (m, 3H); 2.73 (s, 3H); 2.34 (s, 3H); 1.45 (d, 3H);
MS (ES/+): m/z=564 $[M-Cl]^+$.

Example 10

2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(R)-methylamino-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride (10a)
2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-methylamino-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride (10b)

Intermediate 4a (120 mg), methylamine (1M solution in THF - 2.5 mL) and sodium triacetoxyborohydride (65 mg) in dry 1,2-dichloroethane (5 mL) was stirred at 23°C for 2 hours under a nitrogen atmosphere. The solution was washed with a 5% sodium hydrogen carbonate solution (10 mL) and brine (10 mL). The organic layer was dried and concentrated

in vacuo to a residue which was purified by flash chromatography (AcOEt/MeOH 75:25) to give two fractions:

1. diastereoisomer 1 (40 mg - T.l.c. AcOEt/MeOH 7:3 Rf=0.3)
2. diastereoisomer 2 (20 mg) - T.l.c. AcOEt/MeOH 7:3 Rf=0.21)

Example 10a

A solution of diastereoisomer 1 (40 mg) in dry Et2O (3 mL) was treated with hydrochloric acid (1M in Et2O – 0.5 mL) and the resulting solution was stirred at 0 C° for 5 minutes. The solution was concentrated *in vacuo* and the residue was triturated with n-pentane (2 mL) to give the title compound as a white solid (40 mg).

IR (nujol): 3398 (NH_2^+), 1627 (C=O) cm^{-1}.

NMR (d_6-DMSO): δ (ppm) 8.60 (bs, 2H); 7.99 (s, 1H); 7.75 (s, 2H); 7.32 (dd, 1H); 6.99 (dd, 1H); 6.90 (m, 1H); 5.13 (q, 1H); 5.016 (t, 1H); 3.42 (m, 2H); 3.14 (m, 1H); 2.61 (s, 3H); 2.57 (s, 3H); 2.24 (s, 3H); 2.12 (m, 2H); 1.95 (m, 1H); 1.62 (m, 1H); 1.54 (d, 3H).

MS (ES/+): m/z=520 [MH-HCl]

Example 10b

A solution of diastereoisomer B (20 mg) in dry Et2O (3 mL) was treated with hydrochloric acid (1M in Et2O – 0.5 mL). The solution was concentrated *in vacuo* and the residue was triturated with n-pentane (2 mL) to give the title compound as a white solid (20 mg).

IR (nujol): 3398 (NH_2^+), 1658-1650 (C=O) cm^{-1}.

NMR (d_6-DMSO): δ (ppm) 8.60 (bs, 2H); 7.99 (s, 1H); 7.67 (s, 2H); 7.15 (dd, 1H); 6.94 (dd, 1H); 6.83 (m, 1H); 5.30 (q, 1H); 4.18 (dd, 1H); 3.42 (m, 1H); 3.26 (m, 1H); 2.76 (t, 1H); 2.73 (s, 3H); 2.55 (s, 3H); 2.35 (s, 3H); 2.10-2.00 (m, 1H); 1.68 (m, 1H); 1.53 (m, 1H); 1.45 (d, 3H);

MS (ES/+): m/z=520 $[MH\text{-}HCl]^+$.

Example 11

2-(4-Fluoro-2-methyl-phenyl)-4-methylamino-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide hydrochloride (11a and 11b)

A solution of intermediate 3 (150 mg), methylamine (2M in THF - 300μL) and sodium triacetoxyborohydride (100 mg) in dry THF (6 mL) was stirred at r. t. under a nitrogen atmosphere. After 5 hours further methylamine (2M in THF - 300μL) and sodium triacetoxyborohydride (35 mg) were added. After 3 hours the crude solution was quenched with a 5% sodium hydrogen carbonate solution (5 mL) and taken up with AcOEt (5 mL). The aqueous phase was extracted with AcOEt (3 x 15 mL) and the combined organic phases were washed with brine (5 mL). The organic layer was dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (AcOEt/MeOH 85:15) to give 2-(4-fluoro-2-methyl-phenyl)-4-methylamino-piperidine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methylamide in two fractions:

1. diastereoisomer 1 (C-2 and C-4 anti configuration –100 mg);
2. diastereoisomer 2 (C-2 and C-4 syn configuration – 13 mg).

Example 11a (diastereoisomer A)

A solution of diastereoisomer 1 (100 mg) in dry Et2O (3 mL) was treated with hydrochloric acid (1M in Et2O – 220 μL) at 0°C. The resulting solution was stirred under a nitrogen atmosphere for 15 minutes, then it was concentrated *in vacuo*. The residue was triturated with diethyl ether/n-pentane to give the title compound (81 mg) as a white solid.

NMR (d_6-DMSO): δ (ppm) 8.66 (bm, 2H); 7.94 (bs, 1H); 7.65 (bs, 2H); 7.24 (dd, 1H); 6.89 (dd, 1H); 6.79 (dt, 1H); 4.64 (dd, 1H); 4.57 (d, 1H); 4.37 (d, 1H); 3.19 (m, 1H); 3.07 (m, 1H); 2.86 (s, 3H); 2.75 (m, 1H); 2.28 (s, 3H); 2.26 (s, 3H); 1.84 (m, 3H); 1.7 – 1.5 (m, 1H).

MS (ES/+): m/z = 506 $[MH]^+$, 370.

Example 11b (diastereoisomer B)

A solution of diastereoisomer 2 (13 mg) in dry Et2O (2 mL) was treated with hydrochloric acid (1M in Et2O – 30 μL) at 0°C and the resulting solution was stirred under a nitrogen atmosphere for 15 minutes. The solution was concentrated *in vacuo* and the residue was triturated with Et2O /n-pentane to give the title compound (10 mg) as a white solid.

NMR (d_6-DMSO): δ (ppm) 8.65 (bm, 2H); 7.94 (bs, 1H); 7.58 (bs, 2H); 7.19 (dd, 1H); 6.93 (dd, 1H); 6.82 (dt 1H); 4.62 (d, 1H); 4.33 (d, 1H); 4.18 (dd, 1H); 3.49 (m, 1H); 3.25 (bm, 1H); 2.92 (s, 3H); 2.74 (m, 1H); 2.55 (s, 3H); 2.35 (s, 3H); 2.12 –2.06(m, 2H); 1.68 (m, 1H); 1.48 (q, 1H).

MS (ES/+): m/z = 506 $[MH]^+$, 370.

Example 12

4-Amino-2-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide hydrochloride (12a and 12b)

Methanesulphonyl chloride (20 μL) was added to a solution of 2-(4-fluoro-2-methyl-phenyl)-4-hydroxy-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide (intermediate **11a** and **11b** - mixture of syn and anti diastereomers - 85 mg) and TEA (50 μL) in dry THF (5 mL) previously cooled to 0°C under a nitrogen atmosphere. After 1.5 hours, the solution was quenched with brine (4 mL) and extracted with AcOEt (3 x 5 mL). The organic layer was dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (CH/AcOEt 7:3) to give methanesulfonic acid, 1-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-2-(4-fluoro-2-methyl-phenyl)-piperidin-4-yl ester in two fractions:

1. diastereoisomer 1 (11 mg);
2. diastereoisomer 2 (76 mg).

Example 12a (diastereoisomer B)

A solution of diastereoisomer 1 (11 mg) and sodium azide (2 mg) in dry DMF (2 mL) was stirred at 80°C for 4 hours under a nitrogen atmosphere. The crude solution was diluted with AcOEt (5 mL) and washed with cold brine (3 x 5 mL). The organic layer was dried and concentrated *in vacuo* to give the crude 4-azido-2-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide as a semisolid white residue (20 mg) which was treated with triphenylphosphine (10 mg) in dry THF (3 mL) was stirred at r. t. for 48 hours under a nitrogen atmosphere. Then water (3 μL) was added and the mixture was stirred for further 48 hours. The crude solution was taken up with AcOEt (5 mL) and

washed with brine (5 mL). The organic layer was dried and concentrated *in vacuo* to give the crude 4-amino-2-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide. This residue was dissolved in dry Et2O (2mL), treated with hydrochloric acid (1M in Et2O – 100 λL) at 0°C and the resulting solution was stirred under a nitrogen atmosphere for 15 minutes. The solution was concentrated *in vacuo* and the residue was triturated with Et2O/n-pentane to give the title compound (9 mg) as a pale yellow solid.

NMR (d_6-DMSO): δ (ppm) 9.92 (bs, 1H); 7.9-7.7 (b, 3H); 7.58 (s, 2H); 7.29 (m, 1H); 6.94 (m, 1H); 6.82 (m, 1H); 4.39 (m, 1H); 4.34 (d, 1H); 4.16 (d, 1H); 3.50 (m, 1H); 3.31 (m, 1H); 2.93 (m, 1H); 2.92 (s, 3H); 2.33 (s, 3H); 2.05-1.65 (m, 4H).

MS (ES/+): m/z = 492 $[M-Cl]^+$.

Example 12b (diastereoisomer A)

A solution of diastereoisomer 2 (75 mg) and sodium azide (13 mg) in dry DMF (5 mL) was stirred at 80°C for 4 hours under a nitrogen atmosphere. The solution was diluted with AcOEt (5 mL) and washed with cold brine (3 x 5 mL). The organic layer was dried and concentrated *in vacuo* to give the crude 4-azido-2-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide as a semisolid white residue (80 mg). This residue (60 mg) treated with - triphenylphosphine (30 mg) in dry THF (6 mL) was stirred at r. t. for 48 hours under a nitrogen atmosphere. Then, water (3 μL) was added and the mixture was stirred for further 48 hours. The crude solution was taken up with AcOEt (5 mL) and washed with brine (5 mL). The organic layer was dried and concentrated *in vacuo* to give the crude 4-amino-2-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide.

This residue was dissolved in dry Et2O (2 mL), treated with hydrochloric acid (1M in Et2O – 300 μL) at 0°C and the resulting solution was stirred under a nitrogen atmosphere for 15 minutes. The solution was concentrated *in vacuo* and the residue was triturated with Et2O/n-pentane to give the title compound (10 mg) as a white solid.

NMR (d_6-DMSO): δ (ppm) 7.98 (s, 1H); 7.9-7.7 (b, 3H); 7.74 (s, 2H); 7.31 (m, 1H); 6.98 (m, 1H); 6.90 (m, 1H); 4.93 (t, 1H); 4.57 (d, 1H); 4.42 (d, 1H); 3.56 (m, 1H); 3.30 (m, 1H); 3.13 (m, 1H); 2.83 (s, 3H); 2.26 (s, 3H); 2.02-1.62 (m, 4H).

MS (ES/+): m/z = 492 $[M-Cl]^+$, 475 $[M-HCl-NH_3]^+$.

Example 13

4-(R)-Cyclobutylamino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis)-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride (13a)

4-(S)-Cyclobutylamino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis)-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride (13b)

A solution of intermediate **4a** (120 mg), cyclobutylamine (20.4 μL) and sodium triacetoxyborohydride (75.5 mg) in dry 1,2-dichloroethane (10 mL) was stirred at 23°C for 4 hours under a nitrogen atmosphere. The solution was washed with a 5% sodium hydrogen carbonate solution (10 mL) and brine (10 mL). The organic layer was dried and concentrated *in vacuo* to a residue that was purified by flash chromatography (AcOEt/MeOH 9:1) to give:

1. diastereoisomer 1 (55.9 mg - T.l.c.: AcOEt/MeOH 8:2 Rf=0.44),
2. a mixture of the two diastereoisomer (33.3 mg)
3. diastereoisomer 2 (22.9 mg - T.l.c.: AcOEt/MeOH 8:2 Rf=0.3).

Example 13a

A solution of diastereoisomer 1 (53.5 mg) in dry Et2O (10 mL) was treated with hydrochloric acid (1M in Et2O – 2 mL) and the resulting solution was stirred at 23°C for 30 minutes. The solution was concentrated *in vacuo* to give the title compound as a white solid (54 mg).
M.p.: 68-70°C (dec).
IR (nujol): 3400, 3000-2400 (NH_2^+), 1637 (C=O) cm^{-1}.
NMR (d_6-DMSO): δ (ppm) 8.79 (bs, 2H); 7.99 (s, 1H); 7.74 (s, 2H); 7.28 (dd, 1H); 6.97 (dd, 1H); 6.89 (dd, 1H); 5.13 (q, 1H); 4.98 (bt, 1H); 3.83 (m, 1H); 3.45-3.35 (m, 2H); 3.11 (m, 1H); 2.62 (s, 3H); 2.25 (s, 3H); 2.18 (2m, 4H); 1.92-1.76 (2m, 2H); 1.61 (m, 2H); 1.53 (d, 3H); 1.24 (m, 1H); 0.84 (m, 1H).
MS (ES/+): m/z=560 $[MH-HCl]^+$.

Example 13b

A solution of diastereoisomer 2 (21.2 mg) in dry Et2O (5 mL) was treated with hydrochloric acid (1M in Et2O – 2 mL). The resulting mixture was stirred at 23°C for 15 minutes, then filtered to give the title compound as a whitish solid (22 mg).
M.p.: 211-213°C (dec).
IR (nujol): 3400-2500 (NH_2^+), 1664 (C=O) cm^{-1}.
NMR (d_6-DMSO): δ (ppm) 9.07 (bs, 2H); 7.98 (bs, 1H); 7.65 (bs, 2H); 7.13 (m, 1H); 6.93 (m, 1H); 6.81 (m, 1H); 5.27 (m, 1H); 4.17 (m, 1H); 3.80 (bm, 1H); 3.4-3.3 (m, 2H); 2.77 (m, 1H); 2.72 (m, 3H); 2.33 (s, 3H); 2.17 (m, 4H); 2.07-1.99 (m, 2H); 1.8-1.4 (m, 2H); 1.44 (d, 3H); 1.24 (m, 1H); 0.84 (m, 1H).
MS (ES/+): m/z=560

Example 14

4-(R)-Cyclopropylamino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride (14a)

4-(S)-Cyclopropylamino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride (14b)

A solution of intermediate **4a** (120 mg), cyclopropylamine (16.6 µL) and sodium triacetoxyborohydride (78.2 mg) in dry 1,2-dichloroethane (5 mL) was stirred at 23°C for 2 hours under a nitrogen atmosphere. The solution was washed with a 5% sodium hydrogen carbonate solution (10 mL) and brine (10 mL). The organic layer was dried and concentrated *in vacuo* to a residue that was purified by flash chromatography (AcOEt/MeOH 85:15) to give three fractions:

1. diastereoisomer 1 (59.5 mg - T.l.c.: AcOEt/MeOH 7:3 Rf=0.40),
2. a mixture of the two diastereoisomer (20.0 mg)
3. diastereoisomer 2 (32.0 mg - T.l.c.: AcOEt/MeOH 7:3 Rf=0.37).

Example 14a

A solution of diastereoisomer 1 (59.5 mg) in dry Et2O (5 mL) was treated with hydrochloric acid (1M in Et2O – 1 mL) and the resulting solution was stirred at 23°C for 30 minutes. The solution was concentrated *in vacuo* to give the title compound as a white solid (59.5 mg).
IR (nujol): 3404, (NH_2^+), 1639 (C=O) cm^{-1}.
NMR (d_6-DMSO): δ (ppm) 8.86 (bs, 2H); 8.77 (bs, 1H); 8.00 (s, 1H); 7.76 (s, 2H); 7.34 (dd, 1H); 6.99 (dd, 1H); 6.92 (dt, 1H); 5.15 (q, 1H); 5.04 (bt, 1H); 3.66 (bm, 1H); 3.42 (bm, 1H); 3.14 (dt, 1H); 2.74 (bm, 1H); 2.63 (s, 3H); 2.25 (s, 3H); 2.19 (bm, 2H); 2.02 (bm, 1H); 1.68 (m, 1H); 1.55 (d, 3H); 0.84 (bm, 2H); 0.79 (bm, 2H).
MS (ES/+): m/z=546 $[MH\text{-}HCl]^+$.

Example 14b

A solution of diastereoisomer 2 (32.0 mg) in dry Et2O (5 mL) was treated with hydrochloric acid (1M in Et2O – 1 mL). The resulting mixture was stirred at 23°C for 15 minutes, then filtered and treated with further diethyl ether to give the title compound as a whitish solid (20 mg).
IR (nujol): 3383 (NH_2^+), 1650 (C=O) cm^{-1}.
NMR (d_6-DMSO): δ (ppm) 9.00 (sa, 2H); 7.99 (s, 1H); 7.67 (s, 2H); 7.15 (dd, 1H); 6.94 (dd, 1H); 6.83 (m, 1H); 5.29 (q, 1H); 4.21 (dd, 1H); 2.73 (s, 3H); 2.45 (m, 2H); 2.35 (s, 3H); 2.9-2.2 (m, 2H); 1.8-0.7 (m, 8H); 1.45 (d, 3H).
MS (ES/+): m/z=546 $[MH\text{-}HCl]^+$.

Example 15

2-(R)-(4-Fluoro-2-methyl-phenyl)-4-[methyl-(1-methyl-piperidin-4-yl)-amino]-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide hydrochloride

A solution of intermediate 4a (120 mg), 1-methyl-4-(methylamino)-piperidine (34.6 μL) and sodium triacetoxyborohydride (75.5 mg) in dry 1,2-dichloroethane (2.5 mL) was stirred at 23°C overnight under a nitrogen atmosphere. The solution was washed with a 5% sodium hydrogen carbonate solution (10 mL) and brine (10 mL). The organic layer was dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (AcOEt/MeOH from 10:0 to 1:1) to give the 2-(4-fluoro-2-methyl-phenyl)-4-[methyl-(1-methyl-piperidin-4-yl)-amino]-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide (43 mg as a mixture of diastereoisomer A and diastereoisomer B) which was dissolved in dry Et2O (5 mL) and treated with hydrochloric acid (1M in Et2O – 1mL). The resulting mixture was stirred at 23°C for 30 minutes, then it was concentrated *in vacuo*. The residue was triturated with Et2O to give the title compound (25 mg) as a white solid and as a mixture of diastereoisomer A / diastereoisomer B 60:40.
NMR (d_6-DMSO): δ (ppm) 10.40 and 9.50 (2bs, 2H); 7.90 (d, 1H); 7.73 and 7.67 (2s, 2H); 7.30 and 7.22 (2bt, 1H); 6.94-6.75 (2m, 2H); 5.31 and 5.11 (2q, 1H); 5.00 and 4.24 (2bd, 1H); 2.36 and 2.27 (2s, 3H); 1.53 and 1.46 (2d, 3H); 2.74-2.61 (6s, 9H); 3.40-1.75 (14m, 16H).
MS (ES/+): m/z=617 $[MH\text{-}HCl]^+$.

Example16

4-Benzylamino-2-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide (16a and 16 b)

A solution of intermediate 2 (30 mg), benzylamine (7.5 µL), acetic acid (6µL) and sodium triacetoxyborohydride (22 mg) in dry 1,2-dichloroethane (2 mL) was stirred at r.t. under a nitrogen atmosphere. After 0.5 hours further benzylamine (7.5 µL) and sodium triacetoxyborohydride (22 mg) were added. After 1.5 hours the crude solution was quenched with a 1N potassium hydroxide solution (2 mL) and taken up with AcOEt (5 mL). The aqueous phase was extracted with AcOEt (3 x 5 mL) and the combined organic phases were washed with brine (5 mL). The organic layer was dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (AcOEt/MeOH 9:1) to give two fractions:

1. diastereoisomer A (24 mg - T.l.c.: AcOEt/MeOH 9:1 Rf=0.45),
2. diastereoisomer B (10 mg - T.l.c.: AcOEt/MeOH 9:1 Rf=0.3).

Example 16a (diastereoisomer A)

NMR (d_6-DMSO): δ (ppm) 7.95 (bs, 1H); 7.60 (bs, 2H); 7.20 (m, 6H); 6.90 (m, 1H); 6.79 (m, 1H); 4.64 (d, 1H); 4.30 (d, 1H); 4.10 (m, 1H); 3.65 (bs, 2H); 3.15 (m, 1H); 2.90 (s, 3H); 2.65 (m, 1H); 2.35 (m, 1H); 2.25 (s, 3H); 1.90 (m, 2H); 1.6 – 1.5 (m, 2H).

MS (ES/+): m/z = 582 $[MH]^+$, 446.

Example 16b (diastereoisomer B)

NMR (d_6-DMSO): δ (ppm) 7.93 (bs, 1H); 7.58 (bs, 2H); 7.25 (m, 6H); 6.88 (dd, 1H); 6.77 (dt, 1H); 4.62 (d, 1H); 4.32 (d, 1H); 4.09 (dd, 1H); 3.71 (s, 2H); 3.40 (m, 1H); 2.90 (s, 3H); 2.65 (m, 1H); 2.59 (m, 1H); 2.31 (s, 3H); 1.95(m, 2H); 1.43 (m, 1H); 1.20 (m, 1H).

MS (ES/+): m/z = 582 $[MH]^+$, 446.

Example 17

4-[(1,3-Dioxolan-2-yl)-methyl]-amino-2-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide

A solution of intermediate 3 (10 mg), 2-(aminomethyl)-1,3-dioxolane (2.09 mg), sodium triacetoxyborohydride (6.45 mg) and acetic acid (1,7 µl) in dry 1,2-dichloroethane (400 µl) was stirred at 23°C for 18 hours. The solution was diluted with DCM (1 mL) and washed with a 0.5N solution of sodium hydroxide (1 mL). The two phases were separated using a Whatman filter tube with polypropylene filter and the organic solution was then passed through a SCX cartridge (Varian, 100mg). The cartridge was washed with methanol (3 mL) and the product was then released by adding a 0.25M solution of ammonia in MeOH (1 mL) and washing with MeOH (1 mL). The solution was concentrated *in vacuo* to give the title compound (7.0 mg) as a mixture of diastereoisomers – A and B in ratio 70:30.

Diastereoisomer A:

NMR ($CDCl_3$): δ (ppm) 7.75 (bs, 1H); 7.53 (s, 2H); 7.25 (dd, 1H); 6.85-6.78 (m, 2H); 4.96 (dd, 1H); 4.57 (d, 1H); 4.43 (d, 1H); 5.01 (t, 1H); 3.99 (m, 2H); 3.90 (m, 2H); 2.88 (s, 3H); 2.34 (s, 3H); 2.84 (d, 2H); 3.48-3.38 and 3.18-3.08 and 2.14-1.50(m, 7H).

MS (ES/+): m/z=577.

Diastereoisomer B: NMR ($CDCl_3$): δ (ppm) 7.75 (bs, 1H); 7.67 (bs, 1H); 7.42 (s, 2H); 7.17 (dd, 1H); 6.85-6.78 (m, 2H); 4.28 (dd, 1H); 4.65 (d, 1H); 4.37 (d, 1H); 4.99 (t, 1H); 3.99 (m, 2H); 3.90 (m, 2H); 2.96 (s, 3H); 2.43 (s, 3H); 2.86 (d, 2H); 3.48-3.38 and 3.18-3.08 and 2.14-1.50(m, 7H).

MS (ES/+): m/z=577.

Example 18

4-(R)-N-2-Fluoroethyl-N-methylamino)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide hydrochloride

Formaldehyde (37% in water – 208 µL), 10% palladium over charcoal (34mg) and 2 drops of acetic acid were added to a solution of Example 7a (98 mg) in MeOH (5 mL). The mixture was stirred at r.t. under a hydrogen atmosphere for 1 hour, then it was filtered though celite and concentrated *in vacuo*. The residue was purified by flash chromatography (AcOEt/MeOH 9:1) to give the 4-(R)-(N-2-fluoroethyl-N-methylamino)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide (85 mg - T.l.c.: AcOEt/MeOH 8:2, Rf=0.37). This material was dissolved in dry Et2O (5 mL), treated with hydrochloric acid (1M in Et2O – 0.5 mL) and the resulting solution was stirred under a nitrogen atmosphere for 15 minutes. The solution was concentrated *in vacuo* and the residue was triturated from Et2O /n-pentane to give the title compound as a white solid (85 mg).

IR (nujol): 3348 (NH^+), 1628 (C=O) cm^{-1}.

NMR (d_6-DMSO): δ (ppm) 8.9 (bs, 1H); 7.99 (s, 1H); 7.78 (s, 2H); 7.35 (dd, 1H); 7.0 (dd, 1H); 6.92 (dt 1H); 5.08 (bt, 1H); 4.73 (d, 2H); 4.58 (d, 1H); 4.43 (d, 1H); 3.65 (bm, 1H); 3.42-3.3 (m, 3H); 3.11 (dt, 1H); 2.81 (s, 3H); 2.5 (m, 3H); 2.27 (s, 3H); 2.17 (m, 1H); 2.11 (m, 1H); 2.06 (m, 1H); 1.69 (m, 1H).

MS (ES/+): m/z = 552 $[MH\text{-}HCl]^+$.

Example 19

4-(R)-(Carbamoylmethyl-amino)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide hydrochloride (19a)

4-(S)-(Carbamoylmethyl-amino)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide hydrochloride (19a)

A solution of intermediate **10** (120 mg), glycinamide hydrochloride (81 mg) and TEA (102 µL) in dry 1,2-dichloroethane (2 mL) and acetonitrile (2 mL) was stirred at r.t. for 1h under a nitrogen atmosphere. Then sodium triacetoxyborohydride (78 mg) was added and the mixture was stirred at 23°C for 18 hours. The solution was washed with a 5% sodium hydrogen carbonate solution (10 mL) and extracted with DCM (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (AcOEt/MeOH 8:2) to give two fractions:

1. diastereoisomer 1 (47 mg – T.l.c.: AcOEt/MeOH 8:2, Rf=0.22);
2. diastereoisomer 2 (35 mg – T.l.c.: AcOEt/MeOH 8:2 Rf=0.13).

Example 19a

A solution of diastereoisomer 1 (47 mg) in dry Et2O (5 mL) was treated with hydrochloric acid (1M in Et2O – 0.1 mL). The resulting mixture was stirred at 0°C for 15 minutes, then filtered to give the title compound as a yellow solid (41.5 mg).

M.p.: 130-1°C.

IR (nujol): 3325 (NH_2^+), 1697 (C=O) cm^{-1}.

NMR (d_6-DMSO): δ (ppm) 8.97 (bs, 1H); 8.92 (bs, 1H); 7.98 (s, 1H); 7.85 (s, 1H); 7.78 (s, 2H); 7.62 (s, 1H); 7.34 (td, 1H); 7.0 (dd, 1H); 6.91 (td, 1H); 5.1 (t, 1H); 4.57 (d, 1H); 4.41 (d, 1H); 3.74 (bs, 2H); 3.59 (bs, 1H); 3.46 (bd, 1H); 3.09 (t, 1H); 2.78 (s, 3H); 2.26 (s, 3H); 2.19 (m, 1H); 2.03 (m, 2H); 1.66 (m, 1H).

MS (ES/+): m/z=549 $[M+H]^+$.

Example 19b

A solution of diastereoisomer 2 (35 mg) in dry Et2O (5 mL) was treated with hydrochloric acid (1M in Et2O – 0.1 mL). The resulting mixture was stirred at 0°C for 15 minutes, then filtered to give the title compound as a yellow solid (27 mg).

M.p.: 100-1°C.

IR (nujol): 3300-3100 (NH_2^+), 1695 (C=O) cm^{-1}.

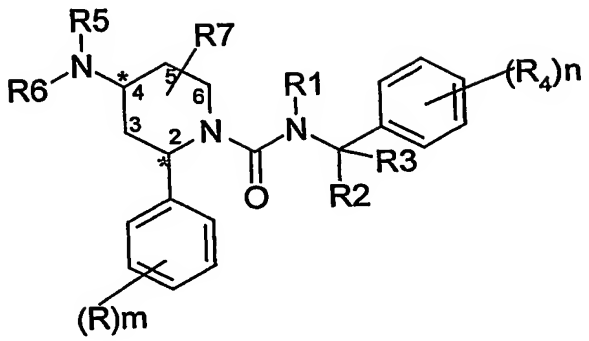
NMR (d_6-DMSO): δ (ppm) 8.97 (bd, 2H); 7.94 (s, 1H); 7.81 (s, 1H); 7.59 (s, 3H); 7.18 (t, 1H); 6.94 (d, 1H); 6.83 (t, 1H); 4.64 (d, 1H); 4.33 (d, 1H); 4.17 (dd, 1H); 3.71 (bm, 2H); 3.51 (d, 1H); 3.41 (m, 1H); 2.92 (s, 3H); 2.72 (t, 1H); 2.34 (s, 3H); 2.11 (d, 1H); 2.05 (d, 1H); 1.77 (m, 1H); 1.59 (m, 1H).

MS (ES/+): m/z=549 $[M+H]^+$.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

Claims

1. A compound of formula (I)



(I)

wherein

R represents halogen or C_{1-4} alkyl ;

R_1 represents hydrogen or C_{1-4} alkyl;

R_2 represents hydrogen, C_{1-4} alkyl or R2 together with R_3 represents a C_{3-7} cycloalkyl;

R_3 represents hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl or C_{3-6} alkenyl ; or R_1 and R_3 together with nitrogen and carbon atom to which they are attached respectively represent a 5 to 6 membered heterocyclic group;

R_4 represents trifluoromethyl, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethoxy or halogen;

R_5 represents hydrogen, phenyl, C_{3-7} cycloalkyl, $CONR_8R_9$, a saturated 5 to 7 membered heterocyclic group, a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or R_5 represents a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms, or R_5 is C_{1-6} alkyl optionally substituted by one or two groups selected from fluorine, phenyl hydroxy, amino, dimethylamino, aminocarbonyl, C_{1-4} alkoxy or trifluoromethyl;

R_6 represents hydrogen or C_{1-4} alkyl;

R_7 represents hydrogen, a halogen, a C_{1-4} alkyl or COR_{10};

R_8 and R_9 are independently hydrogen or C_{1-4} alkyl;

R_{10} represents hydrogen, hydroxy, amino, methylamino, dimethylamino a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms; m or n are independently zero or an integer from 1 to 3; and pharmaceutically acceptable salts and solvates thereof.

2. A compound selected from:

4-(R,S)-2,2,2-Trifluoroethyl)-amino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;

4-(S)-(2,2-Dimethyl-propylamino)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;

4-(S)-Ethylamino-2-(R)-4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;

4-(S)-Dimethylamino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide ;
4-(S)-Dimethylamino-2-(R)-4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide;
4-(S)-(2-Fluoroethyl)-amino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis)-trifluoromethyl-phenyl)-ethyl]-methylamide ;
4-(S)-(N-2-Fluoroethyl-N-methylamino)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide;
4-(S)-(2-Fluoro-ethylamino)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide;
2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-(2-methoxyethylamino)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;
2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-methylamino-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;
2-(4-Fluoro-2-methyl-phenyl)-4-methylamino-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide;
4-(S)-Cyclobutylamino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis)-trifluoromethyl-phenyl)-ethyl]-methylamide;
4-(S)-Cyclopropylamino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;
2-(R)-(4-Fluoro-2-methyl-phenyl)-4-[methyl-(1-methyl-piperidin-4-yl)-amino]-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;
4--Benzylamino-2-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide;
4-[(1,3-Dioxolan-2-yl)-methyl]-amino-2-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide;
4-(S)-(Carbamoylmethyl-amino)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide;
and enantiomers, pharmaceutically acceptable salts and solvates thereof.

3. A compound as claimed in claim 1 or 2 for use in therapy.

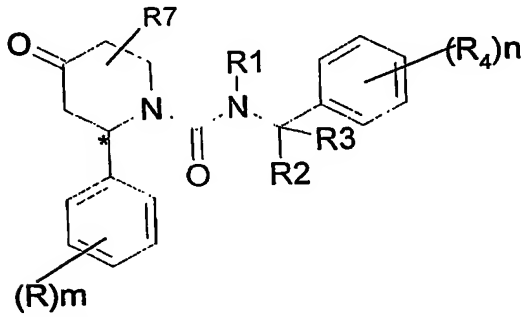
4. The use of a compound as claimed in claim 1 or 2 in the preparation of a medicament for use in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins.

5. The use of a compound as claimed in claim 1 or 2 for use in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins

6. A pharmaceutical composition comprising a compound as claimed in claim 1 or 2 in admixture with one or more pharmaceutically acceptable carriers or excipients.

7. A method for the treatment of a mammal, including man, in particular in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins, comprising administration of an effective amount of a compound as claimed in claim 1 or 2.

8. A process for the preparation of a compound as claimed in claim 1 or 2, which comprises reacting a compound of formula (II),



(II)

R_5R_6NH (III)

with amine (III) in the presence of a suitable metal reducing agent, followed where necessary or desired by one or more of the following steps

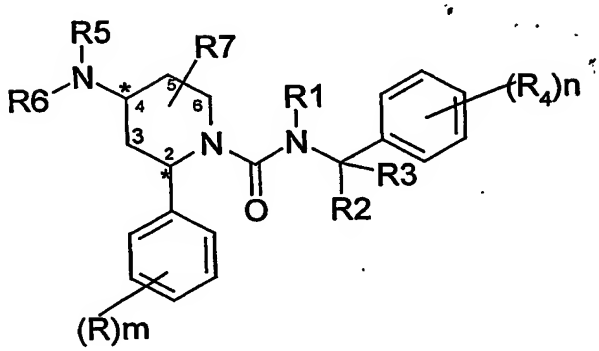
i) removal of any protecting group;

ii) isolation of the compound as a salt or a solvate thereof;

iii) separation of a compound of formula (I) or derivative thereof into the enantiomers thereof.

Abstract

The present invention relates to amine derivatives of formula (I)



(I)

wherein

R represents halogen or C_{1-4} alkyl;

R_1 represents hydrogen or C_{1-4} alkyl;

R_2 represents hydrogen, C_{1-4} alkyl or R2 together with R_3 represents a C_{3-7} cycloalkyl;

R_3 represents hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl or C_{3-6} alkenyl; or R_1 and R_3 together with nitrogen and carbon atom to which they are attached respectively represent a 5 to 6 membered heterocyclic group;

R_4 represents trifluoromethyl, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethoxy or halogen;

R_5 represents hydrogen, phenyl, C_{3-7} cycloalkyl, $CONR_8R_9$, a saturated 5 to 7 membered heterocyclic group, a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or R_5 represents a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms, or R_5 is C_{1-6} alkyl optionally substituted by one or two groups selected from fluorine, phenyl hydroxy, amino, dimethylamino, aminocarbonyl, C_{1-4} alkoxy or trifluoromethyl;

R_6 represents hydrogen or C_{1-4} alkyl;

R_7 represents hydrogen, a halogen, a C_{1-4} alkyl or COR_{10};

R_8 and R_9 are independently hydrogen or C_{1-4} alkyl;

R_{10} represents hydrogen, hydroxy, amino, methylamino, dimethylamino a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms; m or n are independently zero or an integer from 1 to 3; and pharmaceutically acceptable salts and solvates thereof, the process for their preparation and their use in the treatment of condition mediated by tachykinins.